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SYNTHESIS OF 2,5-DISUBSTITUTED TETRAHYDROFURANS CATALYZED BY PALLADIUM(0)

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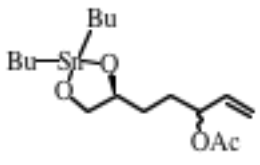
Abstract - A stereoselective cyclization of an allylic ester to 2,5-disubstituted tetrahydrofurans catalyzed by palladium(0) is demonstrated. In this cyclization, acetoxy heptenol (**6a**) having a free hydroxy group prefered *trans* isomer to *cis* isomer. By the use of the protected acetoxy heptenol (**6b**), the *cis* selectivity was observed. The stereoselectivity was enhanced by the use of DPPIO ligand.

Substituted oxygen heterocycles including substituted tetrahydrofuran (THF) and tetrahydropyran (THP) rings have been found in polyether antibiotics and other natural products, and methods for the construction of their structural units in a stereocontrolled fashion have attracted current attention.[1] Electrophilic cyclization to the olefins and nucleophilic cleavage of epoxides with hydroxy group have been used for the construction of these structural units, while transition metal-catalyzed cyclization is also recognized as an effective approach to preparation of these compounds.[2] Actually, Pd(II)-catalyzed intramolecular alkoxypalladation has been known to be a well-established method.[3] However, there have been very few published methods for the stereoselective cyclization to 2,5-disubstituted tetrahydrofurans catalyzed by Pd(0).[4] Trost and Tenaglia have reported that cyclic stannylene diether (**1**) including an allylic ester unit is easily converted into 2,5-disubstituted tetrahydrofuran (**2**) in the presence of Pd(0) in good yield, but with less satisfactory diastereoselectivity (Figure).[4a] Here, we report



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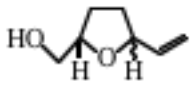

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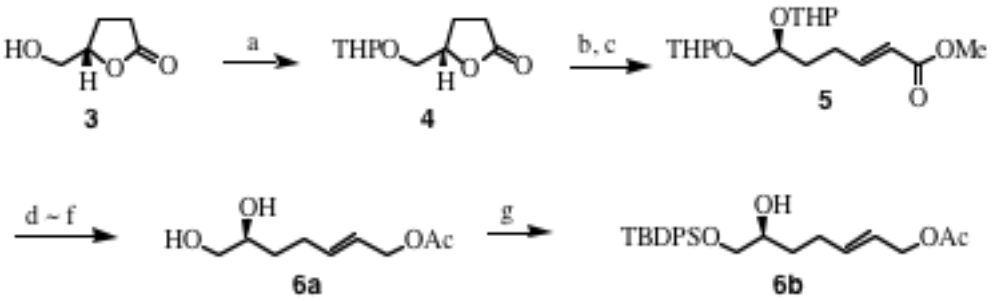
Figure

stereoselective construction of the 2,5- disubstituted THF ring by the allylic substitution reaction.

Allylic esters (**6a** and **6b**) were easily prepared from the hydroxy lactone (**3**) obtained from L-glutamic acid[5] as shown in Scheme. After protection of the hydroxy group with THP , the protected lactone (**4**) was transformed in a one-pot reaction into α,β-unsaturated ester (**5**) in 77% yield by the use of the Takacs' method.[6] The reduction of the ester was carried out with DIBALH at -78 °C to give the corresponding allyl alcohol, which was treated with Ac_2O in pyridine followed by deprotection of the THP groups with TsOH in MeOH at room temperature to give the desired diol (**6a**). The selective protection of the primary hydroxy group was achieved by the treatment of *tert*-butyldiphenylsilyl chloride (TBDPSCl) and imidazole in DMF at room temperature to provide another allyl ester (**6b**).

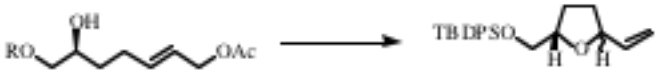


a) DHP, PPTS, CH_2Cl_2, rt, 1 h, 83%; b) DIBALH, THF, -78°C, 15 min then $(EtO)_2POCHLiCOOEt$, -78°C, rt, 17.5 h; c) DHP, TsOH, CH_2Cl_2, rt, 19 h, 77% from **4**; d) DIBALH, toluene, -78°C, 30 min; e) Ac_2O, Py, rt, 9.5 h; f) TsOH, MeOH, rt, 4 h, 38% from **5**; g) TBDPSCl, imidazole, DMF, rt, 2 h, 72%.

Scheme

The results of the intramolecular allylic substitution reaction are listed in Table. Treatment of diol (**6a**) with 4 mol% bis(dibenzylideneacetone)palladium ($Pd(dba)_2$) and 20 mol% Ph_3P gave a volatile THF derivative (**2**), which was converted into **7** with TBDPSCl and imidazole without purification. The *cis*- and *trans*- isomers were isolated by SiO_2 column chromatography and its stereochemistry was determined by the NOE experiment. The stereoselectivity of this reaction was very similar to the previous results reported by Trost (Entry 1).[4a] Also, no cyclization products derived from the primary alcohol to give a THP ring were detected.[4a] The use of $(o\text{-tolyl})_3P$ having a large corn angle favored inducing a *cis* derivative rather than a *trans* derivative.[4b] Unfortunately, this reaction was incomplete after stirring for 60 h at room temperature and then heating for 12 h at 60 ˚C. (Entry 2). The use of $n\text{-}Bu_3P$ and addition of metal salts or a base (silver salts and pyridine) were not effective to improve the stereoselection. Since it is well-known that the use of chiral ligands causes the asymmetric induction in the allylic substitution reaction, we examined the reagent-control condition for improvement of the diastereoselectivity. 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), known to be one of the

Table Pd(0)-catalyzed cyclization to 2,5-disubstituted THF (**7**)[a)]



6a : R = H ; **6b** : R = TBDPS **7**

Entry	Substrate	Ligand (mol%)	Yield (%)	*cis* : *trans*
1	**6a**	Ph_3P (20)	74[b)]	34 : 66
2	**6a**	(*o*-tolyl)$_3$P (20)	28[b,c)]	57 : 43
3	**6a**	(*R*)-BINAP (5)	0	-
4	**6a**	(*S*)-BINAP (5)	0	-
5	**6a**	(*R*)-(*S*)-PPFA (5)	72[b)]	40 : 60
6	**6a**	(*S*)-(*R*)-PPFA (5)	74[b)]	29 : 71
7	**6a**	(+)-9-PBN (10)	74[b)]	29 : 71
8	**6a**	(-)-9-PBN (10)	74[b)]	53 : 47
9	**6a**	(+)-DPPIO (5)	48[b)]	52 : 48
10	**6a**	(-)-DPPIO (5)	83[b)]	23 : 77
11	**6b**	Ph_3P (20)	85	63 : 37
12	**6b**	(+)-DPPIO (5)	96	81 : 19
13	**6b**	(-)-DPPIO (5)	98	45 : 55

a) All reaction were performed using 4 mol% $Pd(dba)_2$ inTHF under N_2 or 12 - 24 h at rt. b) After protection of alcohol with TBDPSCl. c) The reaction was carried out at rt for 60 h then 60°C for 12 h.

most effective ligands in asymmetric synthesis, however, did not work as a catalyst in our systems (Entries 3, 4). *N,N*-Dimethyl-1-[2-(diphenylphosphino)ferrocenyl]ethylamine (PPFA),[7] 2,6-dimethyl-9-phenyl-9-phospabicyclo[3,3,1]nonane (9-PBN)[8] and 2-(2-diphenylphosphinophenyl)-4-isopropyl-1,3-oxazoline (DPPIO)[9] gave the desired THF derivative (**7**) with acceptable yields, and (-)-DPPIO was an effective ligand for the enforcement of *trans* stereoselection while less improvement of *cis* stereoselection was observed in any ligands. Surprisingly, remarkable reversal of diastereoselectivity was observed by the use of **6b**, which afforded **7** in 85% yield in a ratio of 63:37(*cis*:*trans*) even though Ph_3P was used (Entry 11). Furthermore, this *cis* stereoselection was enhanced by a (+)-DPPIO ligand resulting in the ratio of 81:19 (Entry 12). The reason for this reverse diastereoselectivity is unclear, but the presence of a hydroxy group might influence the transition state and the stereoselectivity might be strongly dependent upon the structure of substrate.

In conclusion we reported here a stereoselective synthesis of 2,5-disubstituted tetrahydrofurans catalyzed by Pd(0). Further synthetic studies using this cyclization are under way.

EXPERIMENTAL

General Procedure. Optical rotations were taken with a JASCO DIP-140 polarimeter. IR spectra were taken with a JASCO FT/IR 230 spectrophotometer. MS were taken with a JEOL JMA 2000 mass spectrometer. ^{1}H NMR spectra were taken with a JEOL JNM-A 400 spectrometer in $CDCl_3$, and tetramethylsilane was used as internal standard. ^{13}C NMR spectra were taken with a JEOL JNM-A 400 spectrometer in $CDCl_3$, and $CDCl_3$ was used as internal standard.

(2*S*,5*E*)-7-Acetoxy-5-heptene-1,2-diol (6a). Under N_2, to a solution of **5** (15.7 g, 44 mmol) in toluene (150 mL) at -78 °C was added dropwise 1.5 M DIBALH in toluene (73 mL, 110 mmol) over a period of 30 mim. The solution was stirred an additional 30 min at -78 °C, and Na_2SO_4•$10H_2O$ was added. After warmed to rt and stirred for 1 h, the suspension was filtered through a celite pad. Removal of the solvent gave the crude allyl alcohol. To a solution of the above allyl alcohol in pyridine (150 mL) at 0 °C was added Ac_2O (16.6 mL, 176 mmol). The solution was warmed to rt and stirred for 9.5 h. After removal of pyridine *in vacuo*, water was added and the mixture was extracted with EtOAc. The combined organic layers were washed 1 M HCl, saturated $NaHCO_3$ and saturated brine, and dried (Na_2SO_4). Removal of the solvent gave the crude allyl acetate. To a solution of the above allyl acetate in MeOH (200 mL) at rt was added TsOH•H_2O (840 mg, 4.4 mmol). After 4 h at rt, MeOH was removed *in vacuo*. Saturated $NaHCO_3$ was added, the mixture was extracted with EtOAc, and the combined organic layers were washed saturated brine and dried (Na_2SO_4). Removal of the solvent and flash chromatography of the residue on SiO_2 (200 g, EtOAc - hexane (4 : 1)) gave **6a** (3.19 g, 38% from **5**) as an oil. $[\alpha]^{22}_{D}$ -2.0 ° (*c* 1.13, $CHCl_3$); IR neat (cm^{-1}) 3390, 2939, 2858, 1732, 1446, 1385, 1365, 1242, 1028, 972, 868; ^{1}H NMR δ (ppm) 5.79 (dt, 1H, *J* = 15.4, 6.6 Hz), 5.62 (dt, 1H, *J* = 15.4, 6.4 Hz), 4.52 (d, 2H, *J* = 6.4 Hz), 3.73 (m, 1H), 3.67 (dd, 1H, *J* = 11.0, 3.2 Hz), 3.46 (dt, 1H, *J* = 11.0, 7.6 Hz), 2.3 - 2.1 (m, 2H), 2.06 (s, 3H), 2.0 - 1.4 (br s, 2H), 1.56 (m, 2H); ^{13}C NMR δ (ppm) 170.6, 135.4, 124.6, 71.6, 66.7, 65.1, 32.2, 28.3, 24.9, 21.0; Anal. Calcd for $C_9H_{16}O_4$: C, 57.43; H, 8.57. Found: C, 57.44; H, 8.77.

(2*S*,5*E*)-7-Acetoxy-1-*tert*-butyldiphenylsiloxy-5-hepten-1-ol (6b). To a solution of **6a** (470.5 mg, 2.5 mmol) in DMF (15 mL) at rt were added imidazole (357.5 mg, 5.25 mmol) and TBDPSCl (0.68 mL, 2.63 mmol). After 2 h at rt, water was added and the mixture was extracted with EtOAc - hexane (1 : 1). The combined organic layers were washed with water and saturated brine, dried (Na_2SO_4), and concentrated. Flash chromatography of the residue on SiO_2 (120 g, EtOAc - hexane (1 : 6)) gave **6b** (770.1 mg, 72%) as

an oil. $[\alpha]^{22}_{D}$ +6.2 ° (*c* 0.51, $CHCl_3$); IR neat (cm^{-1}) 3477, 3070, 2931, 2858, 1739, 1589, 1471, 1427, 1362, 1232, 1113, 970, 877 823, 741, 702; ^{1}H NMR δ (ppm) 7.66 (m, 4H), 7.5 - 7.3 (m, 6H), 5.74 (dt, 1H, *J* = 15.3, 6.6 Hz), 5.55 (dtt, 1H, *J* = 15.3, 6.5, 1.1 Hz), 4.49 (dd, 2H, *J* = 6.6, 1.1 Hz), 3.71 (m, 1H), 3.65 (dd, 1H, *J* = 10.0, 3.4 Hz), 3.49 (dd, 1H, *J* = 10.0, 7.3 Hz), 3.41 (br d, 1H, *J* = 3.4), 2.3 - 2.0 (m, 2H), 2.04 (s, 3H), 1.6 - 1.4 (m, 2H), 1.07 (s, 9H); ^{13}C NMR δ (ppm) 171.3, 135.5, 135.5, 133.1, 129.8, 127.8, 124.3, 71.2, 67.9, 65.1, 31.9, 28.2, 26.8, 21.0, 19.3; Anal. Calcd for $C_{25}H_{34}O_4Si$: C, 70.38; H, 8.03. Found: C, 70.18; H, 8.27.

General procedure for Pd(0)-catalyzed cyclization. Under nitrogen, to a solution of $Pd(dba)_2$ (11.5 mg, 0.02 mmol) and monodentate ligand (10 or 20 mol%) or bidentate ligand (5 mol%) in THF (1 mL) was added a solution of diol **6a** (94.1 mg, 0.5 mmol) or monoalcohol **6b** (213.3 mg 0.5 mmol) in THF (1 mL). After stirring at room temperature for 12-24 h, the mixture was filtered through a celite pad. After removal of the solvent, to the crude mixture of **2** were added DMF (3 mL), imidazole (204 mg, 3 mmol) and TBDPSCl (0.39 mL, 1.5 mmol). After stirring for 6 h at rt, water was added and the mixture was extracted 3 times with EtOAc - hexane (1 : 1). The combined organic layers were washed with water and saturated brine, dried (Na_2SO_4), and concentrated. Purification of crude **7** was performed by flash chromatography on SiO_2 (25 g, Et_2O-hexane (1:24)) to afford *cis*-**7** and *trans*-**7**.

(2*S*,5*R*)-2-(*tert*-Butyldiphenylsiloxy)methyl-5-vinyltetrahydrofuran (*cis*-7). *Rf* 0.64 (Et_2O - hexane (1 : 6); $[\alpha]^{22}_{D}$ +1.9 ° (*c* 1.12, $CHCl_3$); IR neat (cm^{-1}) 3070, 2958, 2931, 2858, 1589, 1471, 1427, 1113, 989, 922, 823, 740, 702; MS (EI) *m*/*z* 309 (M^+-*tert* -Bu); ^{1}H NMR δ (ppm) 7.68 (m, 4H), 7.39 (m, 6H), 5.84 (ddd, 1H, *J* = 17.1, 10.5, 6.6 Hz), 5.24 (dt, 1H, *J* = 17.1, 1.2 Hz), 5.06 (dt, 1H, *J* = 10.5, 1.2 Hz), 4.31 (m, 1H), 4.09 (m, 1H), 3.70 (dd, 1H, *J* = 10.2, 4.4 Hz), 3.63 (dd, 1H, *J* = 10.2, 5.5 Hz), 2.1 - 1.85 (m, 3H), 1.75 - 1.6 (m, 1H), 1.06 (s, 9H); ^{13}C NMR δ (ppm) 139.4, 135.6, 133.6, 129.6, 127.6, 115.3, 80.8, 79.7, 66.4, 31.8, 28.0, 26.8, 19.3; Anal. Calcd for $C_{23}H_{30}O_2Si$: C, 75.36; H, 8.25. Found: C, 75.37; H, 8.41.

(2*S*,5*S*)-2-(*tert*-Butyldiphenylsiloxy)methyl-5-vinyltetrahydrofuran (*trans*-7). *Rf* 0.69 (Et_2O - hexane (1 : 6)); $[\alpha]^{22}_{D}$ +5.1 ° (*c* 1.12, $CHCl_3$); IR neat (cm^{-1}) 3072, 2958, 2931, 2858, 1589, 1471, 1427, 1113, 997, 922, 823, 741, 702 ; MS (EI) *m*/*z* 309 (M^+-*tert*-Bu); ^{1}H NMR δ (ppm) 7.68 (m, 4H), 7.38 (m, 6H), 5.84 (ddd, 1H, *J* = 17.1, 10.2, 6.3 Hz), 5.22 (dt, 1H, *J* = 17.1, 1.3 Hz), 5.08 (dt, 1H, *J* = 10.2, 1.3 Hz), 4.41 (dd, 1H, *J* = 13.6, 6.3 Hz), 4.18 (m, 1H), 3.69 (dd, 1H, *J* = 10.5, 4.6 Hz), 3.65 (dd, 1H, *J* = 10.5, 5.1 Hz), 2.15 - 1.95 (m, 2H), 1.95 - 1.80 (m, 1H), 1.7 - 1.6 (m, 1H) 1.06 (s, 9H); ^{13}C NMR δ (ppm) 139.3, 135.6, 133.7,

129.6, 127.6, 115.1, 80.3, 79.3, 66.5, 32.3, 28.0, 26.8, 19.3; Anal. Calcd for $C_{23}H_{30}O_2Si$: C, 75.36; H, 8.25. Found: C, 75.21; H, 8.43.

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