HETEROCYCLES, Vol. 63, No. 5, 2004, pp. 1017 - 1021
Received, 12th February, 2004, Accepted, 2nd March, 2004, Published online, 8th March, 2004

PALLADIUM(II)-CATALYZED STEREOCONTROLLED CYCLIZATION *VIA* HEMIACETAL INTERMEDIATES: TOTAL SYNTHESIS OF 5-EPI-PRELACTONE C

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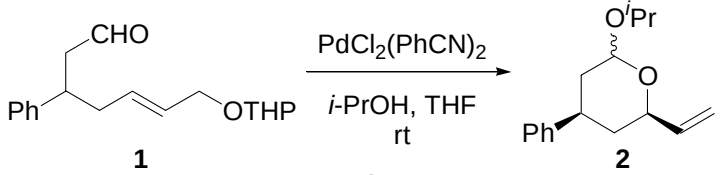
Abstract – Palladium(II)-catalyzed cyclization of 3,7-dihydroxy-4-methyl-5-octenal derivative was carried out to give 2,3,4,6-tetrasubstituted tetrahydropyran with stereoselective 1,3-chirality transfer in net retention of stereochemistry. The cyclized product was converted into 5-epi-prelactone C.

The polysubstituted δ-lactone structure can be found in many natural products, particularly polyketide macrolide producing microorganisms. It is a very important to develop synthetic methodology for the stereoselective construction of the δ-lactone structure, so many synthetic methods have been reported.[1]
We have reported an intramolecular substitution of an allylic alcohol by a heteroatom using a palladium catalyst without activation of the allylic alcohol.[2] And we recently developed a cyclization *via* a hemiacetal intermediate using a palladium catalyst and found a stereoselective method for construction of trisubstituted tetrahydropyran (Scheme 1).[3] In connection with the palladium-catalyzed heterocyclization, we applied the method to synthesis of a natural product having a δ-lactone structure.

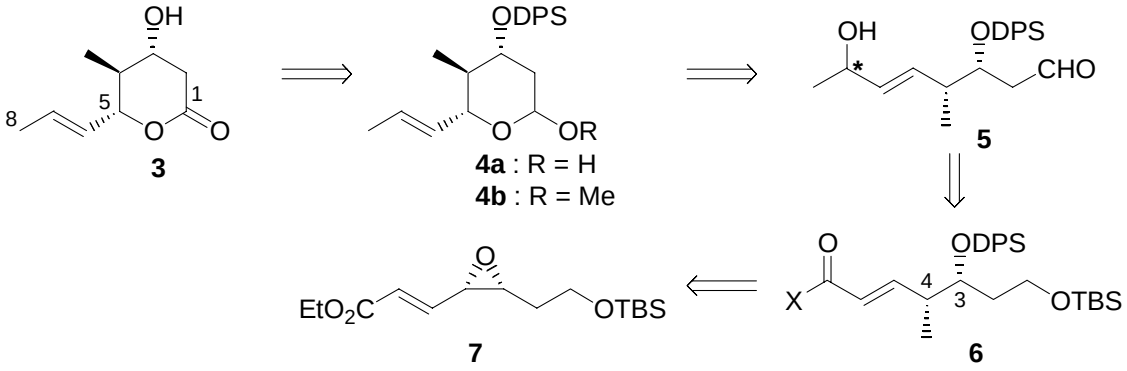


1 **2**

Scheme 1

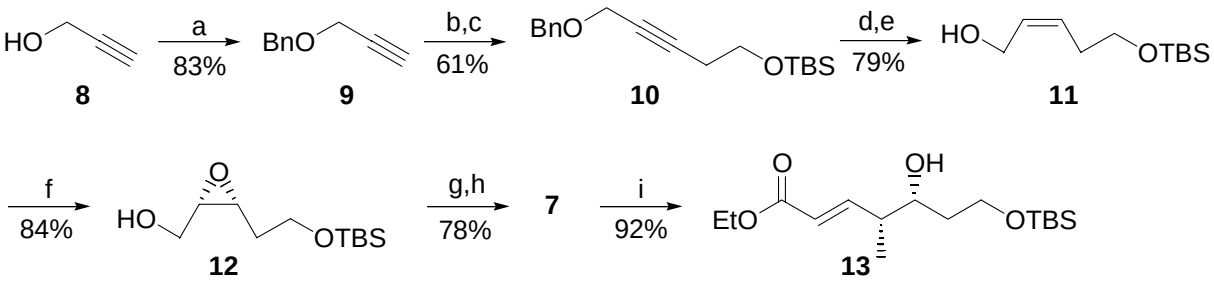
We planned the synthesis of (+)-prelactone C,[4] which comprises an important class of highly functionalized chiral δ-lactones and was isolated from the concanamycin-producing *Streptomyces* sp.[5]

Our retrosynthetic analysis of (+)-prelactone C (**3**) is shown in Scheme 2. Prelactone C would be synthesized *via* oxidation of the hemiacetal (**4a**) (R = H) which might be prepared from the acetal (**4b**) (R = Me) through an acidic treatment. The construction of **4b** could be achieved by the palladium-catalyzed heterocyclization of the aldehyde (**5**) derived from ketone (**6**) (X = Me) through an asymmetric reduction of the carbonyl group. The *syn* silyl ether (**6**) having the C3 and C4 stereogenic centers was readily obtainable by using the stereospecific methylation reaction of the γ,δ-epoxyacrylate (**7**) with trimethylaluminum in the presence of water.[6] The chiral epoxyacrylate (**7**) was readily accessible from the *cis*-5-*t*-butyldimethylsilyloxy-2-penten-1-ol *via* the Katsuki-Sharpless asymmetric epoxidation[7] followed by a Wittig reaction.



Scheme 2

First, the *syn* alcohol (**6**) (X = OEt) was prepared (Scheme 3). Protection of propargyl alcohol (NaH, BnBr, 83% yield) furnished the benzyl ether (**9**). Treatment of **9** with *n*-BuLi and ethylene oxide and protection of the resulting alcohol (TBSCl) afforded the TBS ether (**10**) (61% yield, two steps). Catalytic hydrogenation of the triple bond with Lindlar catalyst followed by removal of the benzyl group gave the *Z*-allylic alcohol (**11**) (79% yield, two steps). The allylic alcohol (**11**) was subjected to Katsuki-Sharpless asymmetric epoxidation with (+)-DET resulting in formation of the α-epoxide (**12**) in 84% yield and 97% ee.[8]

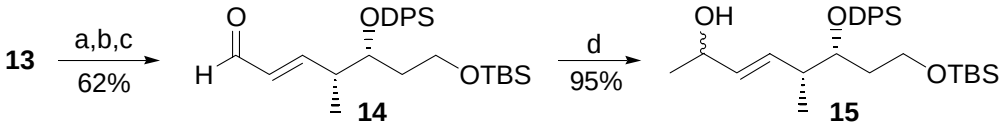


Scheme 3. *Reagents and conditions*: (a) BnBr, NaH, THF; (b) BuLi, ethylene oxide, THF; (c) TBSCl, imidazole, DMF; (d) H_2, 5% Pd/$CaCO_3$, EtOH; (e) Na / NH_3, THF; (f) (+)-DET, Ti(O*i*-Pr)$_4$, TBHP, CH_2Cl_2, -20 ^oC; (g) $(COCl)_2$, DMSO, CH_2Cl_2 then Et_3N; (h) $(EtO)_2POCH_2CO_2Et$, NaH, THF; (i) Me_3Al, H_2O, CH_2Cl_2, -30 ^oC.

The Swern oxidation of the epoxy alcohol (**12**) ($(COCl)_2$, DMSO then Et_3N) followed by the Horner-Emmons reaction of the resulting aldehyde furnished the *trans*-γ,δ-epoxyacrylate (**7**) (78% yield,

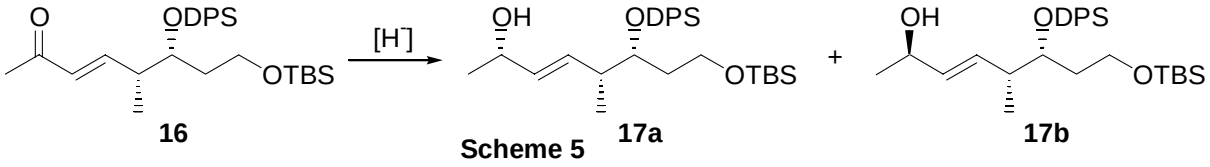
two steps). Methylation of **7** with Me_3Al (10 equiv.) cleanly proceeded in the presence of water (6 equiv.) giving the *syn* compound (**13**) as the sole product in 92% yield.

Protection of the hydroxy group (**13**) (TBDPSCl), reduction of the ester (DIBAL-H), and the Swern oxidation of the resulting alcohol afforded the enal (**14**) (62% yield, three steps). 1,2-Addition of the enal (**14**) with MeMgI furnished the alcohol (**15**) (95% yield). The diastereoselectivity of the addition was 1 : 1.



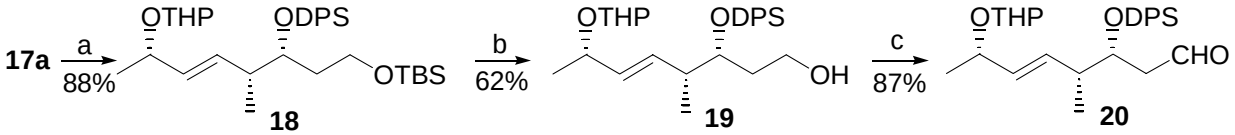
Scheme 4. *Reagents and conditions*: (a) TBDPSCl, Et_3N, DMAP; (b) DIBAL-H, THF; (c) $(COCl)_2$, DMSO, CH_2Cl_2 then Et_3N; (d) MeMgI, THF

The absolute configuration of the C-7 position is crucial to induce the desired stereochemistry on the newly formed C-O bond in the cyclized product (**4**), so stereoselective construction at the C-7 position is indispensable. We planned oxidation of the alcohols (**15**) to the ketone (**16**), and then the ketone (**16**) was stereoselectively reduced to give a diastereometically pure alcohol (**17**). Oxidation of the alcohols (**15**) gave the ketone (**16**) in a quantitative yield. Asymmetric reduction of the enone (**16**) was initially performed with (*S*)-BINAL-H[9] but, somewhat surprisingly, the reduction afforded a mixture of diastereomeric alcohols (**17a**) and (**17b**) (3:2, by ^{1}H NMR). This problem could be overcome by changing the reducing reagent. When **16** was submitted to reduction with (*R*)-Me-CBS / BMS in CH_2Cl_2, **17a** was obtained in good yield (96%) and good diastereoselectivity (**17a**:**17b** = 10:1).[10]



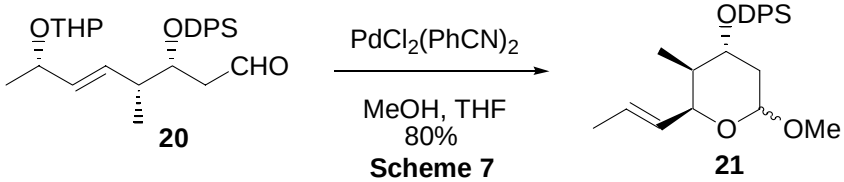
Scheme 5

The cyclized precursor (**20**) was prepared from the alcohol (**17a**). Protection of the hydroxy group (**17a**) (DHP, *p*-TsOH) afforded the THP ether (**18**) (88% yield). Selective deprotection of the TBS group (HF•Py in THF) gave the alcohol (**19**) (62% yield). Finally, IBX oxidation of **19** furnished the aldehyde (**20**).[11]



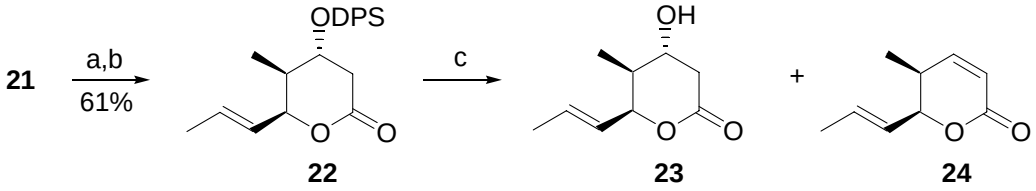
Scheme 6. *Reagents and conditions*: (a) DHP, *p*-TsOH, CH_2Cl_2; (b) HF•Py, THF; (c) IBX, DMSO, THF

Treatment of the aldehyde (**20**) with 10 mol% of $PdCl_2(PhCN)_2$ catalyst and 2.2 equiv. of MeOH in THF furnished the cyclized products (**21**) in 80% yield as a mixture of acetals.



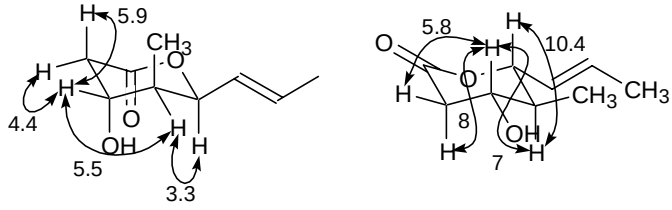
Scheme 7

We proposed the stereochemistry of **21** to lead it to the lactone (**23**). Treatment of **21** under acidic condition (55% AcOH, 70 ^{o}C) followed by IBX oxidation of the resulting hemiacetals afforded the lactone (**22**) (61% yield, two steps). Removal of the DPS group with TBAF gave only 25% to **23** and 70% to β-eliminated product (**24**). Treatment of **22** with HF•Py furnished the alcohol (**23**) in good yield (78%).



Scheme 8. *Reagents and conditions*: (a) 55% AcOH, 70 ^{o}C; (b) IBX, DMSO, THF; (c) HF•Py, THF

The relative stereochemistry of **23** was established by the coupling constant of its ^{1}H NMR spectrum. Surprisingly, the spectra of the obtained compound (**23**)[12] were not found to be identical to those of natural (+)-prelactone C (Figure 1).



5-epi-prelactone C (**23**) prelactone C (**3**)

Figure 1 H-H Couping constants (Hz) of **23** and **3.**

This was not entirely unexpected, as **23** was an epimer at the C-5 position of prelactone C. Our previous results demonstrated that palladium(II)-catalyzed cyclization reaction proceeded stereoselectively with net inversion of configuration.[2] Extension of this methodology to the asymmetric synthesis of (+)-prelactone C is currently being carried out in our laboratories.

In summary, we have demonstrated that intramolecular cyclization *via* a hemiacetal intermediate by using a palladium(II)-catalyst proceeds stereoselectively with net retention of configuration, and we have completed the synthesis of 5-epi-prelactone C.

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12. 5-epi-Prelactone C (**23**): $[\alpha]^{25}_{D}$ –86.6^{o} (*c* 0.5, MeOH); ^{1}H-NMR ($CDCl_3$, 600 MHz) δ : 5.83 (1H, ddq, *J* = 15.4, 1.1, 6.6 Hz), 5.50 (1H, ddq, *J* = 15.4, 7.0, 1.7 Hz), 5.10 (1H, dd, *J* = 7.0, 3.3 Hz), 4.03 (1H, q, *J* = 5.3 Hz), 2.89 (1H, dd, *J* = 18.3, 5.9 Hz), 2.53 (1H, ddd, *J* = 18.3, 4.4, 0.7 Hz), 1.99 (1H, ddq, *J* = 5.5, 3.3, 7.3 Hz), 1.75 (3H, dd, *J* = 6.6, 1.7 Hz), 0.99 (3H, d, *J* = 7.3 Hz); ^{13}C-NMR ($CDCl_3$, 150 MHz) δ : 170.48, 130.42, 126.00, 79.42, 67.82, 38.77, 36.50, 17.80, 11.00; IR (neat) : 3421, 2968, 2921, 1716, 1455, 1367, 1244, 1059, 968, 707 cm^{-1}; EIMS m/z (%): 170 (2) M^{+}, 152 (11); FABMS m/z (%): 171 (12, M^{+}+H).