Synthetic Study of Chiral Dihydrofuran Derivatives *via* Olefin Metathesis: Allylic Oxidation Conditions to a Butenolide

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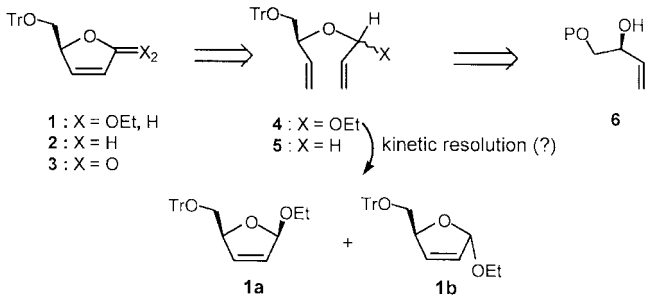
Received June 21, 2001

Keywords : Olefin metathesis, Butenolide, Allylic oxidation, (D)-Mannitol.

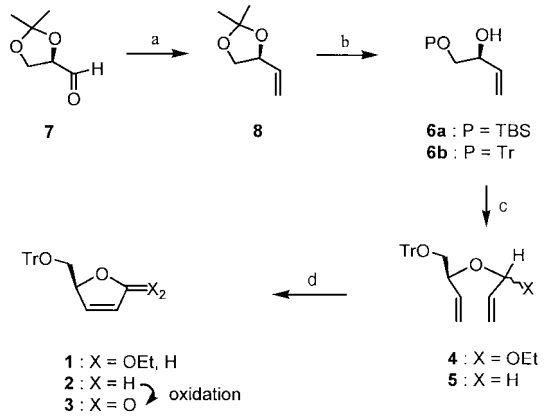
Chiral dihydrofuran derivatives such as α,β-butenolides have served as useful chiral synthons in various natural product syntheses,[1] and many synthetic methods to these chiral intermediates have been described until recently.[2] As we also have been interested in the compounds as potential precursors for C-glycoside synthesis on ribose analogous skeletons,[3] we hoped to develop a new divergent route to the intermediates in a concise manner *via* ring closing olefin metathesis (RCM) reaction. The metathesis reaction has been utilized increasingly in the past few years for the synthesis of various cyclic compounds,[4] however, rarely for the chiral dihydrofuran intermediates. We envisioned optically pure acetals **4** or allyl ether **5** would be a suitable substrate for the skeleton, and especially we wondered whether there would be a little rate difference in the RCM reaction of the epimeric acetals **4** (Scheme 1), that is to say kinetic resolution. The kinetic resolution of **4** would hopefully afford the sterically less hindered α-ethoxy dihydrofuran **1a** as a major product, which should suggest a new selective route to glycosides.



Scheme 1

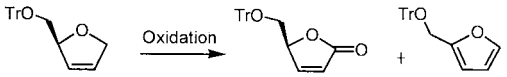
The protected chiral allyl alcohol precursors **6** were prepared through 2,3-*O*-isopropylidene-D-glyceraldehyde starting from (D)-mannitol.[5] The Wittig reaction of the aldehyde with methyl triphenylphosphonium iodide and *n*-BuLi furnished the olefin group. And deprotection of the isopropylidene **8** by treating with CF_3COOH in THF was followed by selective protection of primary hydroxy group using *t*-butyldimethylsilyl chloride in THF or triphenylmethyl chloride to yield the ethers **6** in modest yields (21% for **6a** and 19% for **6b** respectively). Acetal **4** was prepared by reaction of **6b** *via* transketalization with acrolein diethyl acetal[6] in 90% yield as a 4 : 3 mixture and allyl ether **5** was obtained with allyl bromide in 66% yield. Using Grubbs' catalyst (5 mol%) in CH_2Cl_2, the RCM reaction of **4** at room temperature provided the compound **1** as a 4 : 3 mixture, without any change in the ratio, in 68% yield. Lowering the reaction temperature, decreasing the amount of catalyst used, and shortening reaction time did not show any indication of ratio change of compound **1**. Although we expected the steric hindrance between 1,4-disubstituents in the dihydofurane ring should render the rate of RCM different, the result showed practical equivalence of cyclization rate. The same reaction of **5** yielded **2** in 79% yields (Scheme 2).

For the formation of furanone **3**, an acryllic ester derivative from **6** would be a proper precursor for the metathesis reaction, however, several attempts of esterification reaction of **6** yielded only the starting material back. Alternatively, transformation of **2** to **3** by allylic oxidation reaction has been tried (Table 1). Selenium dioxide in dioxane at 90 °C afforded only furane derivative **9** in 40% yield. We assumed the compound was made through formation of an acetal type intermediate and the subsequent elimination catalyzed by trace of acid, preventing further oxidation. So basic media was rather hoped to reduce the elimination reaction of the intermediate. When the complex of CrO_3 : pyridine was used, variable ratios of products **3** and **9** were detected depending on solvent. The addition of base such as Et_3N or $(i\text{-Pr})_2NEt$ to the solvent showed only moderate change in the ratio, however, the enhancement of reagent basicity,



Scheme 2. Reagents: (a) Ph_3PCH_3I, *n*-BuLi, THF (91%); (b) CF_3COOH-H_2O, THF, rt, 12h, then Ph_3CCl, NaH, THF (19%) or TBSCl, NaH, THF (21%); (c) Allyl bromide, NaH, DMF, 60 °C (66%) or CH_2=CHCH$(OEt)_2$, PPTS, toluene, 35 °C, 80 mbar (90%); (d) 5 mol% $Cl_2(PCy_3)_2Ru$=CHPh, CH_2Cl_2, rt.

Table 1. Allylic oxidation of **2**



2 **3** **9**

Reagent (equiv.)	Solvent	Temp. (°C)	Yield (%)[a] of **2** / **3** / **9**
SeO_2 (1.2)	1,4-dioxane	90	22 / **0** / **40**
CrO_3·2Py (6.0)	CH_2Cl_2	40	29 / 29 / 37
CrO_3·2Py (6.0)	Et_3N/CH_2Cl_2	40	38 / 21 / 14
CrO_3·2Py (6.0)	Pyridine	70	13 / 17 / 27
CrO_3·2Py (6.0)	(*i*-Pr)$_2$NEt/ CH_2Cl_2	40	51 / 21 / 22
CrO_3·DMP (20)	CH_2Cl_2	r.t.	6 / **57** / **0**

[a]Isolation yield

changing CrO_3 : pyridine to CrO_3 : DMP (dimethylpiperazine) suppressed the elimination process enough to provide **3** as a single product in 57% yield (Table 1), showing identical spectral data with the known compound. This reaction condition suggested an intriguing route to a furanone from dihydrofurane.

In summary, the dihydrofuran derivatives have been obtained concisely *via* olefin metathesis reaction, and transformation to trityloxymethyl-2-furanone **3** was performed by allylic oxidation using CrO_3 : DMP complex. However, the conceptually expected kinetic resolution in the RCM of **4** was not detected at all.

Experimental Section

General for the selected experiments. ^{1}H NMR spectra were recorded on a Bruker AC 200 spectrometer using tetramethylsilane as an internal standard. Chemical shifts are measured in part per million(d) and coupling constants, *J*, are reported in Hz. All reactions were carried out under nitrogen atmosphere and anhydrous solvents were used.

1,2-Isopropylidene-2-butene 8. *n*-BuLi (21.5 mL, 53.8 mmol) was added slowly to a solution of methyltriphenylphosphonium iodide (19.8 g, 48.9 mmol) in THF (100 mL) at −78 °C. The solution was warmed to rt, and aldehyde **7** (5.3 g, 40.8 mmol) in THF (20 mL) was added. The mixture was stirred at rt for 20h, and diluted with EtOAc (200 mL). The organic layer was washed with brine, dried over $MgSO_4$, and filtrated. The crude product was separated by vacuum distillation to afford 4.77 g of **8** (91%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.80 (m, 1H), 5.15-5.40 (m, 2H), 4.50 (q, *J* = 4.7 Hz, 1H), 4.10 (m, 2H), 1.42 (s, 3H), 1.39 (s, 3H); IR (thin film) 2945, 2827, 1455, 1217, 1063, and 924 cm^{-1}; EIMS *m/z* 128 (M^+).

1-Triphenylmethoxy-but-3-en-2-ol 6b. Trifluoroacetic acid (7.42 mL, 96.3 mmol) and water (5.78 mL, 321 mmol) were added slowly to a solution of compound **8** (4.12 g, 32.1 mmol) in THF (25 mL) at 0 °C. The mixture was stirred at rt for 12 h, neutralized by addition of NaOH (3.85 g, 96.3 mmol), and dried over $MgSO_4$. Filtration followed by concentration afforded a diol intermediate (2.50, 75%), which was used for the next step. NaH (0.272 g, 6.81 mmol) was added to a solution of the diol intermediate (0.5 g, 5.67 mmol) in THF (20 mL) at °C, and the mixture was stirred at rt for 1 h. To this solution was added triphenylmethyl chloride (1.74 g, 6.24 mmol) and the resulting solution was stirred at rt for 20 h. After dilution of the solution with CH_2Cl_2, the organic layer was washed with satíd NH_4Cl solution and dried over $MgSO_4$. Concentration and separation by column chromatography afforded **6b** as a yellow oil (0.70 g, 19.4%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20-7.50 (m, 15H), 5.80 (m, 1H), 5.15-5.25 (m, 2H), 4.22-4.28 (q, *J* = 4.8 Hz, 1H); IR (thin film) 3086, 2870, 1960, 1076 cm^{-1}; EIMS *m/z* 258 (M^+-ph).

2-Trityloxymethyl-2,5-dihydrofuran 2. NaH (0.3 g, 0.9 mmol) was added to a solution of **6b** in DMF (4 mL) at 0 °C, and the solution was stirred at rt for 1 h. To this solution was added allyl bromide (0.159 mL, 1.83 mmol) at rt, and the solution was heated at 60 °C for 15 h. The solution was cooled to rt and diluted with EtOAc, the organic layer was washed with sat'd NH_4Cl solution and brine, and dried over $MgSO_4$. After filtration and concentration, the crude product was separated by silica-gel column chromatography to obtain **5** (0.223 g, 66%), which was readily treated by Grubbsí catalyst, benzylidene-bis(tricyclohexylphosphine)-dichlororuthenium (25 mg, 0.03 mmol), in CH_2Cl_2 (0.1 M solution) at rt. The solution was stirred at rt for 24 hr and concentrated, and the crude product was separated by column chromatography to provide **2** as a white solid: $[\alpha]_D^{25}$ = −53.2 (C=1.8, $CHCl_3$); m.p.=118.6-121.0 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.18-7.57 (m, 15H), 5.95 (dd, *J* = 1.8, 6.0 Hz, 1H), 5.82 (m, 1H), 5.00 (m, 1H), 4.70 (m, 2H), 3.15 (d, *J* = 3.2 Hz, 1H), 3.13 (d, *J* = 3.2 Hz, 1H); IR (thin film) 3056, 2910, 1490, 1088 cm^{-1}.

5-Trityloxymethyl-2-furanone 3. 3.5-Dimethylpyrazole (0.145 g, 1.51 mmol) was added to a rapidly stirring solution of chromium(VI) oxide (0.151 g, 1.51 mmol) in CH_2Cl_2 at −20 °C. To this dark red solution was added compound **2** (25.8 mg, 0.0758 mmol), and the resulting solution was stirred at −20 °C for 2 h. The solution was diluted with CH_2Cl_2, washed with sat'd NH_4Cl solution, and dried over $MgSO_4$. After filtration and concentration, the crude product was separated by silica gel chromatography to afford **3** as a white solid (16 mg, 60%): $[\alpha]_D^{25}$ = −67.2 (C=1.4, $CHCl_3$); m.p.=150.0-153.0 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.20-7.50 (m, 15H), 6.19 (dd, *J* = 2.0, 2.0 Hz, 1H), 5.09 (m, 1H), 3.40 (d, *J* = 5.0 Hz, 2H); IR (thin film) 3100, 1750, 1600 cm^{-1}.

Acknowledgment. This research was financially supported by the Center for Molecular Design and Synthesis at the Korea Advanced Institute of Science and Technology.

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