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ORIGINAL ARTICLE

Practical synthesis of methyl 7-(3-hydroxy-5-oxocyclopent-1-en-1-yl)-heptanoate

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KEYWORDS

Misoprostol;
Dehydrate cyclization;
Friedel-Crafts acylation;
Piancatelli rearrangement

Abstract The key intermediate of misoprostol, methyl 7-(3-hydroxy-5-oxocyclopent-1-en-1-yl)-heptanoate was prepared from commercially available suberic acid in 40% yield over five steps. The key step involved a $ZnCl_2$ catalyzed Friedel-Crafts reaction between furan and 2,9-oxonanedione. Sulfuric acid catalyzed methylation of 8-(furan-2-yl)-8-oxooctanoic acid followed by sequential reduction and $ZnCl_2$ catalyzed Piancatelli rearrangement resulted in the formation of the key intermediate of misoprostol.

1. Introduction

Misoprostol, a 15-deoxy-16-hydroxy-16-methyl prostaglandin E_1 (PGE_1) methyl ester, is developed for the treatment of peptic ulcer disease [1,2] and for labor induction with Mifepristone [3,4]. As a synthetic analog of prostaglandin E_1, misoprostol can avoid the major side effects caused by PGE_1, including fetal bradycardia, pregnant women's emesis, somnolence, and headache. Therefore the synthesis of misoprostol has attracted lot of attention in recent years (Fig. 1).

The two-component coupling strategy is one of the most efficient routes to assemble misoprostol [5–7]. The essential feature of this approach (Fig. 1) is the conjugate addition of 1-indo-4-methyloct-1-en-4-ol **3** [8] to methyl 7-(3-hydroxy-5-oxocyclopent-1-en-1-yl)-heptanoate **2**. To date, a series of researches have been devoted to preparing the key intermediate **2**. In 1976, Kobayash and co-workers [9] found **2** could be prepared mainly by reduction of lactone following selective epoxidation of the olefin in the ring of cyclopentenol giving epoxyalcohol with a double bond in the side chain of the molecule (Scheme 1-a). In 1977, a route developed by Collins et al. [10] revealed an eight-step synthesis of **2** from monomethyl azelate in 12% overall yield (Scheme 1-b). The same year, Kieczykowski et al. [11] employed lithium tert-butyl acetate, 1,5-dibromopentane and lithium imine salts synthesized ketone ester, after sequential three-step transforming intermediate **2** could be obtained in 30% yield (Scheme 1-c). Alternatively, Naora and co-workers [12] used cyclooctanone to do the transformation (Scheme 1-d). In 1994, Holland et al. [13] synthesized of **2** using 2-ethyl-cyclopentanone and methyl-7-

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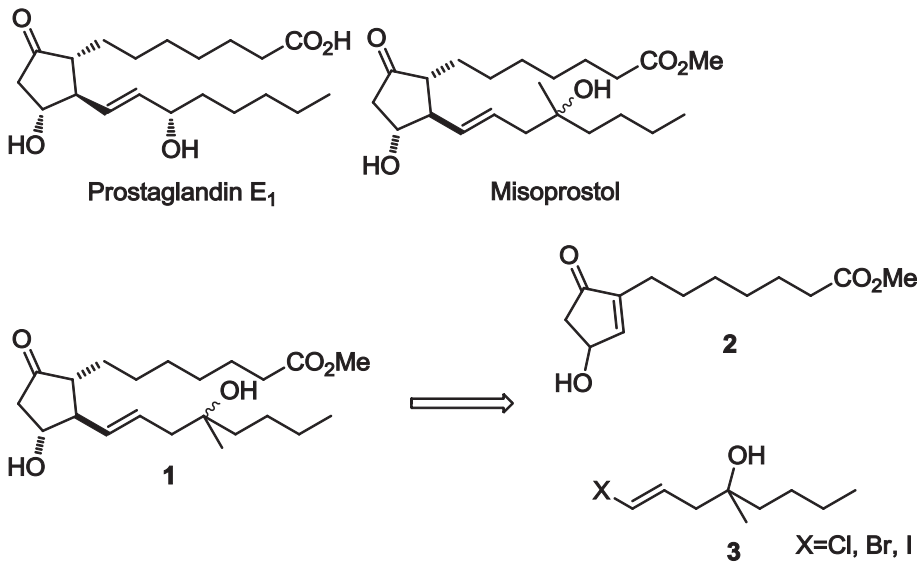
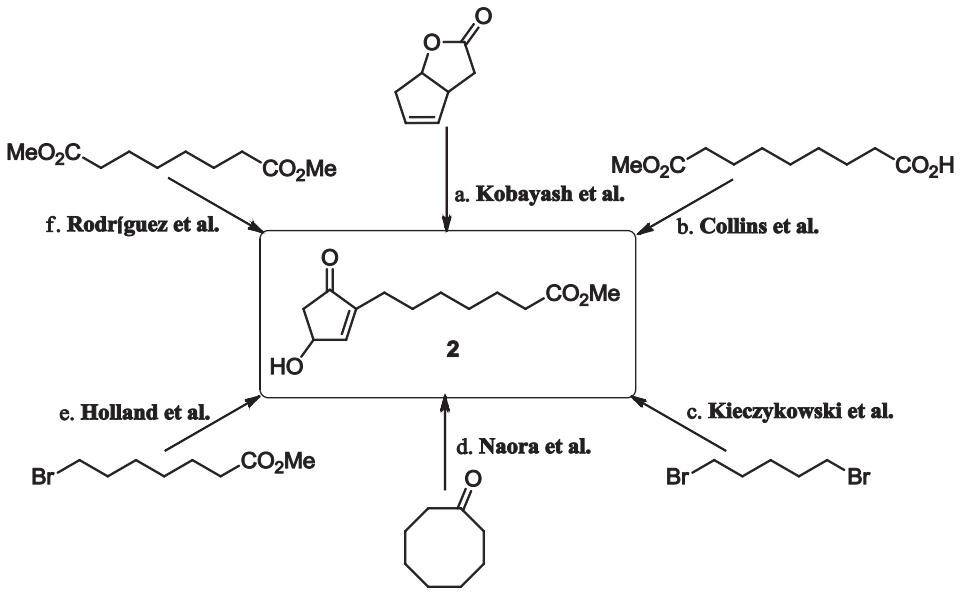


Figure 1 Prostaglandin E_1, misoprostol and two-component coupling retrosynthetic analysis for misoprostol.



Scheme 1 Different protocols for the synthesis of methyl 7-(3-hydroxy-5-oxo-1- cyclopenten-1-yl)-heptanoate **2**.

bromoheptanoate as starting materials in six steps with an overall yield of 23% (Scheme 1-e). Later, Rodríguez et al. [14] reported enzymatic cleavage of dimethyl suberate with porcine pancreatic lipase (PPL) gave a half ester, which was then converted into a mixed anhydride. After reaction with furan, it was reduced with $NaBH_4$ and isomerization to afford **2** (Scheme 1-f). Nevertheless, the majority of these current composite methods bear some disadvantages, including low yields, uneconomic and environmental unfriendly reaction conditions. Herein, we present a practical and efficient synthesis of methyl 7-(3-hydroxy-5-oxocyclopent-1-en-1-yl)-heptano ate from readily available suberic acid, which is not only more environmental friendly, but also can shorten synthesis steps and enhance overall yields.

The synthetic roadmap toward methyl 7-(3-hydroxy-5-oxo cyclopent-1-en-1-yl)-heptanoate **2** was designed on the basis of retrosynthetic analysis shown in Fig. 2. According to Rodríguez's synthesis, **2** could be prepared through a $ZnCl_2$ catalyzed Piancatelli isomerization of methyl 8-(furan-2-yl)-8-hydroxyoctanoate **8** [15], which could be obtained by reduction with $NaBH_4$ from methyl 8-(furan-2-yl)-8-oxooctanoate **7**. Disconnection of the C—C bond linking furan with carbon chain revealed 2,9-oxonanedione **5** as potential intermediates in the synthetic direction. 2,9-oxonanedione itself could be easily prepared from dehydrate cyclization of suberic acid **4**.

2. Experimental

All reagents were purchased from commercial sources and used without purification.

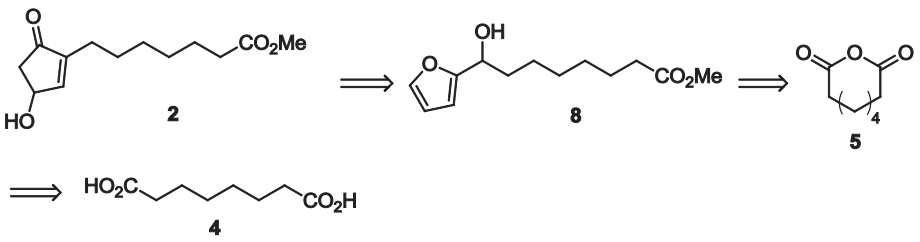


Figure 2 Retrosynthetic analysis for key intermediate **2**.

^{1}H NMR and ^{13}C NMR were obtained from Varian Mercury-Plus 400 MHz (AVANCE Ⅲ 500 MHz) and 100 MHz. Mass spectra were measured with a Thermo Finnigan LCQ Advantage instrument using ESI ionization.

*2.1. Synthesis of 2,9-oxonanedione (**5**) [16]*

Suberic acid (4.998 g, 28.7 mmol) was added to a solution of acetic anhydride (10.0 mL, 106 mmol) at room temperature. The mixture was stirred at 120 °C for 3 h until the acid was not detected. Distillation of the solvent under reduced pressure gave the product as white solid (4.429 g, 99%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.48–2.39 (m, 4H), 1.70–1.59 (m, 4H), 1.42–1.31 (m, 4H).

*2.2. Synthesis of 8-(furan-2-yl)-8-oxooctanoic acid (**6a**) [17]*

To a solution of 2, 9-oxonanedione **5** (142 mg, 0.9 mmol) in CH_3NO_2 (1.0 mL) at 40 °C was added furan (0.17 mL, 2.5 eq.) dropwise and then $ZnCl_2$ (12 mg, 0.1 eq.). When the addition was completed, the mixture was stirred for 1 h until TLC indicated the total consumption of **5**, the reaction mixture was then filtered to remove precipitated suberic acid (56 mg, 35%). The residue was purified by column chromatography on silica gel (hexane/EtOAc = 2:1) to give **6a** (93 mg, 46%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.18 (d, J = 3.2 Hz, 1H), 6.53 (d, J = 1.6 Hz, 1H), 2.83 (t, J = 7.4 Hz, 2H), 2.37 (t, J = 7.4 Hz, 2H), 1.88–1.54 (m, 4H), 1.52–1.42 (m, 4H). MS (ESI): m/z: 247.2 $[M + 23]^+$.

*2.3. One-pot synthesis of 8-(furan-2-yl)-8-oxooctanoic acid (**6a**)*

Suberic acid (4.995 g, 28.7 mmol) was added to a solution of acetic anhydride (10.0 mL, 106 mmol) at room temperature. The mixture was stirred at 120 °C for 3 h until the acid was not detected. Distillation of the solvent under reduced pressure gave the crude product. To a solution of the crude product in CH_3NO_2 (15.0 mL) at 40 °C was added furan (5.2 mL, 2.5 eq.) dropwise and then $ZnCl_2$ (0.375 g, 0.1 eq.). When the addition was completed, the mixture was stirred for 1 h until TLC indicated the total consumption of **5**, the reaction mixture was then filtered to remove precipitate, which was washed with ice water and then dried to give 1.730 g of suberic acid in 35% recovery yield. The filtrate was added with 10% aqueous NaOH (30 mL), extracted with EtOAc (20 mL), then 37% HCl was added in aqueous layer until adjusted pH = 1. The aqueous phase was extracted with DCM (30 mL × 5). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated using a rotary evaporator under reduced pressure to give **6a** (3.105 g, 48%), and the adjusted yield was 74% based on 35% of **4** recovery. This crude product was used in the next step without further purification.

*2.4. Synthesis of 8-(furan-2-yl)-8-oxooctanoic acid (**6a**) from recovered suberic acid*

Following the procedure of one-pot synthesis of 8-(furan-2-yl)-8-oxooctanoic acid, recovered suberic acid (1.730 g, 10.0 mmol) was reacted with acetic anhydride (3.5 mL, 37.0 mmol) afforded 2,9-oxonanedione. The crude product was then reacted with furan (1.8 mL, 2.5 eq.) and $ZnCl_2$ (0.136 g, 0.1 eq.) in CH_3NO_2 (5.0 mL) afforded 1.025 g of **6a** in 46% yield. The adjusted yield was 61% based on 25% of suberic acid recovery.

*2.5. Synthesis of methyl 8-(furan-2-yl)-8-oxooctanoate (**7**) [14]*

Compound **6a** (1.140 g, 5.1 mmol) was dissolved in MeOH (15.0 mL), and added to H_2SO_4 (60 μL, 1.02 mmol) in one portion. After stirring at 100 °C for 4 h, reaction was cooled to ambient temperature. After removal of MeOH under reduced pressure, saturated aqueous $NaHCO_3$ (20 mL) was added to the crude product, then added EtOAc (25 mL) and washed with brine (25 mL). Drying over Na_2SO_4 was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (hexane/EtOAc = 6:1) to give **7** (1.176 g, 97%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.06 (d, J = 3.2 Hz, 1H), 6.41 (dd, J = 3.6 Hz, J = 1.6 Hz, 1H), 3.53 (s, 3H), 2.69 (t, J = 7.4 Hz, 2H), 2.18 (t, J = 7.5 Hz, 2H), δ 1.67–1.43 (m, 4H), δ 1.33–1.18 (m, 4H). MS (ESI): m/z: 261.1 $[M + 23]^+$.

*2.6. Synthesis of methyl 8-(furan-2-yl)-8-hydroxyoctanoate (**8**) [14]*

To a solution of **7** (1.021 g, 4.3 mmol) in MeOH (7 mL) at 0 °C was added $NaBH_4$ (0.238 g, 6.6 mmol), in small portions, until the starting material was completely consumed. After quenching with saturated aqueous NH_4Cl (25 mL) and removal of the MeOH under reduced pressure, the crude product was dissolved in EtOAc (25 mL) and washed with brine (25 mL). Drying over Na_2SO_4 was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (hexane/EtOAc = 6:1) to give **8** (0.950 g, 93%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.28 (m, 1H), 6.28–6.24 (m, 1H), 6.16 (d, J = 3.2 Hz, 1H), 4.59 (t, J = 6.8 Hz,

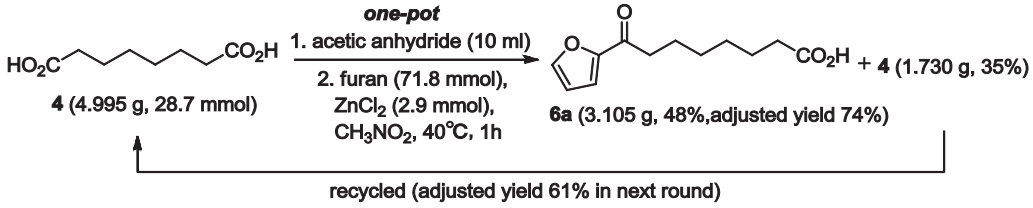
1H), 3.61 (s, 3H), 2.61 (br, 1H), 2.25 (t, J = 7.5 Hz, 2H), 1.83–1.73 (m, 2H), 1.61–1.52 (m, 2H), 1.36–1.21(m, 6H). MS (ESI): m/z: 263. 1 $[M + 23]^+$.

2.7. Synthesis of methyl 7-(3-hydroxy-5-oxocyclopent-1-en-1-yl)-heptanoate (2) [14]

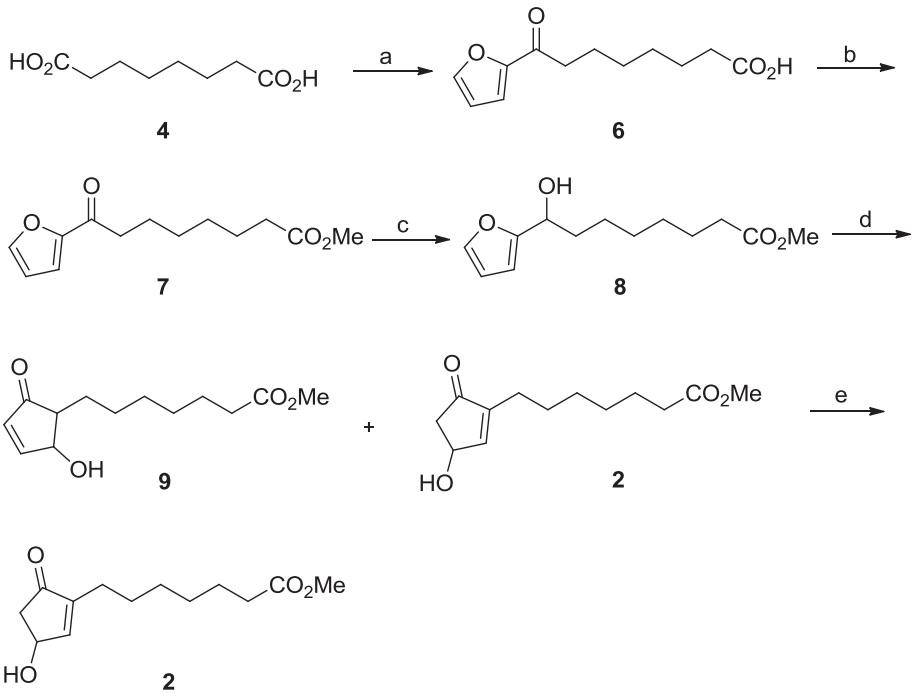
Compound **8** (0.926 g, 3.9 mmol) was dissolved in dioxane (5.5 mL) and water (3.6 mL), stabilized with hydroquinone (1 mg), and added of $ZnCl_2$ (2.035 g, 15.0 mmol). The reaction mixture was refluxed for 6 h. The solvent was removed under reduced pressure and the residue was taken up in EtOAc (30 mL) and washed twice with a saturated aqueous $NaHCO_3$ (15 mL). The EtOAc phase was washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure affording a mixture of **9** and **2**. The crude mixture of **9** and **2** was dissolved in toluene (6.0 mL) and treated with Et_3N (0.35 mL, 2.5 mmol) and anhydrous chloral (23 μL, 0.24 mmol). The solution was stirred until TLC showed completion of the reaction. Removal of the solvent under reduced pressure and the residue was purified by column chromatography on silica gel (hexane/EtOAc = 2:1) to give **2** (0.554 g, 60%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (s, 1H), 4.95 (d, J = 6.4 Hz, 1H), 3.67 (s, 3H), 2.82 (dd, J = 18.4 Hz, J = 6.0 Hz, 1H), 2.35–2.27 (m, 3H), 2.20 (t, J = 7.6 Hz, 2H), 1.76 (s, 1H), 1.68–1.58 (m, 2H), 1.55–1.46 (m, 2H), 1.39–1.31 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.99, 174.09, 155.93, 147.75, 68.50, 51.15, 44.91, 34.07, 28.95, 28.83, 27.22, 24.85, 24.43. MS (ESI): m/z: 263.1 $[M + 23]^+$.

3. Results and discussion

The synthesis of **2** starting from suberic acid proceeded as shown in Scheme 3. In order to examine our hypothesis, our investigation commenced with conversion of suberic acid **4** to 2,9-oxonanedione **5** under different conditions. No desired product was observed when the polar solvents like DMSO and DMF were used (entries 1 and 2, Table 1), but *n*–heptane and dioxane gave **5** in 86% and 96% yield respectively (entries 3 and 4, Table 1). Screening of the other solvents revealed that *o*-dichlorobenzene exhibited similar efficiency in 97% yield

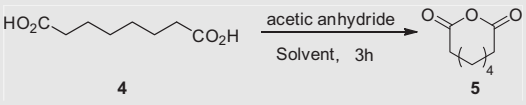


Scheme 2 One-pot synthesis and large-scale of **6a**.



Scheme 3 Synthesis of **2** from suberic acid **4**. Reagents and conditions: a) acetic anhydride, 120°C, 3h; furan, $ZnCl_2$, CH_3NO_2, 40°C, 1h, 48% (74%); b) H_2SO_4, MeOH, 97%; c) $NaBH_4$, MeOH, 0°C, 93%; d) $ZnCl_2$, hydroquinone, dioxane:H_2O (1.5:1), reflux; e) chloral, Et_3N, toluene, r.t., 60%.

Table 1 Dehydrate cyclization of suberic acid **4** using acetic anhydride.[a]



Entry	Solvent	Temp (°C)	Yield (%)[b]
1	DMSO	120	0
2	DMF	120	0
3	*n*-Heptane	98	86
4	Dioxane	100	96
5	*o*-Dichlorobenzene	120	97
6	Chlorobenzene	120	97
7[c]	Acetic anhydride	120	99
8[c]	Acetic anhydride	140	83

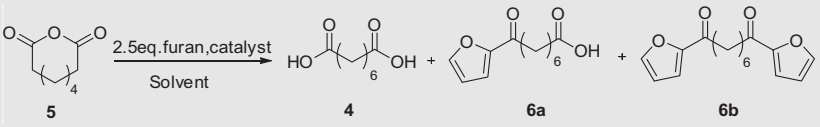
[a] Reaction conditions: **4** (28.7 mmol), acetic anhydride (1.85 eq.) in solvent (20 mL).
[b] Isolated yield.
[c] Acetic anhydride (106 mmol, 3.7eq.) was used as reactant and solvent.

(entry 5, Table 1) comparable to chlorobenzene's yield (entry 6, Table 1). However, when acetic anhydride was used as both reactant and solvent, **5** could be obtained in quantitative yields (entry 8, Table 1). We found increasing the temperature to 140 °C could not improve yields (entry 9, Table 1). Thus the optimized reaction condition was suberic acid **4** with excess acetic anhydride stirring at 120 °C for 3 h gave **5** in 99% yield.

Afterward, we continued the synthesis by optimizing the Lewis acid catalyzed Friedel–Crafts reaction of furan with 2,9-oxonanedione **5**. In the absence of Lewis acid, the reaction produced no ideal acylation product **6a** (entry 1, Table 2). When $AlCl_3$ was used as a catalyst, the reaction afforded **6a** in 10% yield (entry 2, Table 2). Then we screened other Lewis acids such as $FeCl_3$ which afforded **6a** in 41% yield (entry 3, Table 2), considering 21% of starting material suberic acid recovered and could be used in the next round of dehydrate cyclization, the adjusted yields were calculated and used to evaluate the following conditions. While catalysts such as $FeCl_2{\cdot}4H_2O$, $BF_3{\cdot}Et_2O$ and $B(C_6F_5)_3$ only showed low to moderate catalytic activity (entries 4, 5 and 6, Table 2), $ZnCl_2$ successfully enhanced the adjusted yield of **6a** to 57% (entry 9, Table 2). Other trifluoromethanesulfonates, such as $Zn(OTf)_2$, $Mg(OTf)_2$ afforded low to moderate yields (entries 7 and 8, Table 2). Decreasing the equivalent of $ZnCl_2$ could get the similar adjusted yield when used 0.2 equivalent of $ZnCl_2$ (entry 10, Table 2). As for solvents, dichloromethane (DCM), chloroform ($CHCl_3$) and tetrahydrofuran (THF), showed inferior results in comparison with CH_3NO_2, and only low to moderate yields were obtained (entries 11, 12 and 13, Table 2). In addition, conducting the reaction at 40 °C was the better choice compared to 30 °C (43% adjusted yield) and 50 °C (39% adjusted yield) (entries 14 and 15, Table 2). With regard to reaction time, we found prolonging the reaction time from 0.5 h to 1 h could increase the yield of **6a**, and the adjusted yield was enhanced to 71% due to higher recovery of **2** (entries 5 and 16, Table 2).

We then tried to obtain **6a** in one-pot synthesis. As illustrated in Scheme 2, suberic acid **4** (28.7 mmol, 4.995 g) was

Table 2 Friedel–Crafts reaction of 2,9-oxonanedione with furan using Lewis acids catalysts.[a]



Entry	Catalyst (eq.)	Temp (°C)	Solvent	Yield[b] (%) of 6a (4)	Yield[b] (%) of 6b	Adjusted yield[c] (%)
1	–	40	CH_3NO_2	–	–	–
2	$AlCl_3$ (0.2)	40	CH_3NO_2	10 (6)	5	11
3	$FeCl_3$ (0.2)	40	CH_3NO_2	41 (21)	6	52
4	$FeCl_2.4H_2O$ (0.2)	40	CH_3NO_2	37 (17)	7	45
5	$BF_3.Et_2O$ (0.1)	40	CH_3NO_2	22 (20)	7	28
6	$B(C_6F_5)_3$ (0.05)	40	CH_3NO_2	16 (42)	8	28
7	$Zn(OTf)_2$ (0.1)	40	CH_3NO_2	48 (22)	6	62
8	$Mg(OTf)_2$ (0.03)	40	CH_3NO_2	19 (44)	16	34
9	$ZnCl_2$ (0.2)	40	CH_3NO_2	44 (23)	9	57
10	$ZnCl_2$ (0.1)	40	CH_3NO_2	42 (27)	5	58
11	$ZnCl_2$ (0.2)	40	DCM	36 (0)	6	36
12	$ZnCl_2$ (0.2)	40	$CHCl_3$	25 (31)	6	36
13	$ZnCl_2$ (0.2)	40	THF	-	-	-
14	$ZnCl_2$ (0.2)	30	CH_3NO_2	37 (13)	6	43
15	$ZnCl_2$ (0.2)	50	CH_3NO_2	33 (16)	9	39
16[d]	**$ZnCl_2$ (0.1)**	**40**	**CH_3NO_2**	**46 (35)**	**9**	**71**

[a] Reaction conditions: **5** (0.96 mmol), furan (2.5 eq.) in solvent (1 mL) for 0.5 h.
[b] Isolated yield by column chromatography on silica gel (hexane/EtOAc = 2:1).
[c] Yield based on **4** recovery.
[d] The reaction time was 1 h.

first quantitatively cyclized to 2,9-oxonanedione **5**. After distillation under reduced pressure to remove acetic acid and acetic anhydride, the resulting crude product **5** was then dissolved in nitromethane, and stirred with furan (2.5 eq., 71.8 mmol) and zinc chloride (0.1 eq., 2.9 mmol) at 40 °C for 1 h to afford crude products. Subsequent filtration, salification, acidification and extraction afforded **6a** (3.105 g) in 74% adjusted yield, based on 35% of **4** recovery. The recovered **4** could also be reused in the next round to give **6a** in 61% adjusted yield.

After that, sulfuric acid catalyzed methylation of 8-(furan-2-yl)-8-oxooctanoic acid **6a** to afford methyl ester **7** in 97% yield. Then reduction of ketone in MeOH at 0 °C gave hydroxyester **8**. Comparing with 1.1 equivalent (88% yield) and 1.5 equivalent (92% yield) of $NaBH_4$, 1.2 equivalent of $NaBH_4$ afforded **8** in 93% yield. After purification, **8** was used directly in the following isomerization to give **2**. The $ZnCl_2$ catalyzed isomerization was carried out in dioxane/H_2O (1.5:1) and reflux for 6 h, giving a mixture of the hydroxycyclopentenone **9** and **2**. A catalytic amount of chloral catalyzed further isomerization of hydroxycyclopentenone **9** in toluene afforded **2** in 60% yield.

4. Conclusion

In summary, we have developed a simple and efficient method to synthesize methyl 7-(3-hydroxy-5-oxocyclopent-1-en-1-yl)-heptanoate, a valuable key intermediate of misoprostol, via a dehydrate cyclization/Friedel-crafts acylation strategy. Compared with the previous reports, this synthesis was shortened to five steps, and the overall yield was improved to 40%. The process from commercially available starting material suberic acid **4** to a key intermediate **6a** was significantly optimized with good yields and easy workups. Further applications of this approach to build prostaglandin drugs are being conducted in our laboratory.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jscs.2017.01.004.

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