Activation of Carbonyl Function by 1,2-Diol; Novel Asymmetric Spirocyclization based on Acid-catalysed Conjugate Addition

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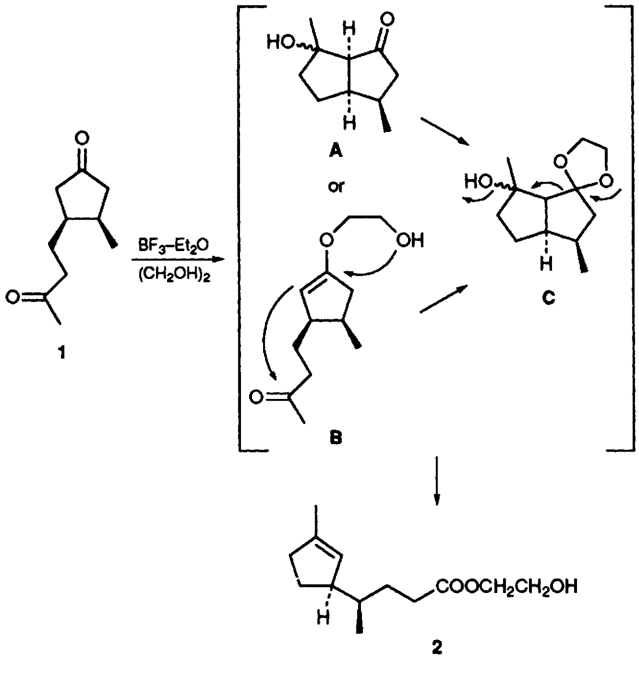
Novel asymmetric spirocyclization of 3-(4-oxopentyl)cyclohex-2-en-1-one **3** based on activation of carbonyl function by BF_3-(*S,S*)-cyclohexane-1,2-diol system has been studied to afford the C_2-symmetric dione (−)-**5** of 85% enantiomeric excess (e.e.) in 86% yield.

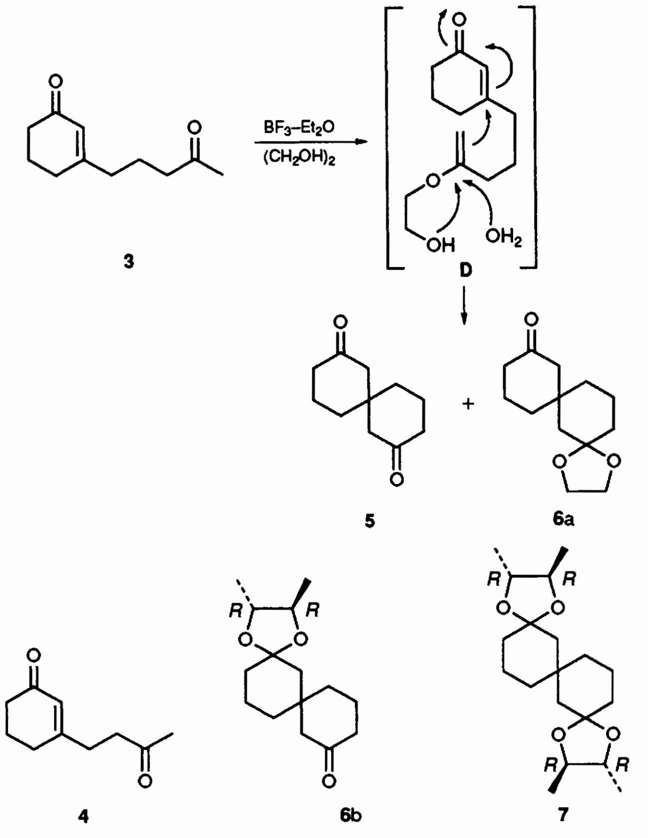
In our previous study of a new ring transformation reaction,[1] which is typically presented in Scheme 1, a new concept for the activation of the carbonyl function with BF_3-1,2-diol system was suggested. We report here a novel spirocyclization based on this new concept and its application to an asymmetric version.

The reaction of **1** with BF_3–Et_2O (7 equiv.) and ethylene glycol (5 equiv.) in CH_2Cl_2 at room temperature afforded the ring transformed product **2** in 69% yield.[1a] We had proposed the reaction mechanisms *via* aldol **A** and subsequent acetal intermediate **C** followed by Grob's fragmentation[2] to afford **2**. The reaction without ethylene glycol afforded neither **2** nor the intermediary **A**, but starting **1** was recovered; this result suggested the new intermediate **B** for aldol condensation at the first stage. That is to say, ethylene glycol might act for both activation of the carbonyl function and subsequent Grob's fragmentation in this ring transformation.

In application of the new concept that activation of the carbonyl function as an enol ether provides a new type of nucleophile, spirocyclization[3] of **3** and **4** was studied. Reaction of **3** with BF_3–Et_2O (7 equiv.) in CH_2Cl_2 at room temp. was so slow that no change was observed after 24 h. After being stirred for 3 days, a small amount of the desired spirocyclic diketone **5**[3a] (30%) was obtained accompanied with recovery of **3** (60%). On the other hand, the reaction in the presence of ethylene glycol (5 equiv.) was obviously accelerated to afford **5** (52%) and monoethylene acetal **6a** (19%) after being stirred



Scheme 1

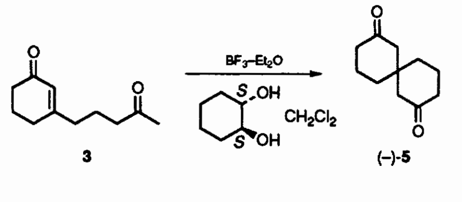


Scheme 2

for 1.5 h at room temp. The structure of C_2-symmetric **5** was confirmed by spectroscopic analyses.† Reaction of **4** under the same conditions resulted in recovery of the substrate. These results were rationalized based on Baldwin's rule.[4] That is to say, cyclization of **3** could be considered as favourable 6-(*enolendo*)-*exo-trig* and that of **4** as unfavourable 5-(*enolendo*)-*exo-trig*.

The above desired result of **3** prompted us to apply this novel spirocyclization into asymmetric version by using optically active 1,2-diols such as (*R*,*R*)-butane-2,3-diol and (*R*,*R* or *S*,*S*)-cyclohexane-1,2-diol.[5] The reaction of **3** with BF$_3$–Et$_2$O (7 equiv.) and (*R*,*R*)-butane-2,3-diol (3 equiv.) at room temp. afforded (+)-**5** (12%) of 25% e.e. and the corresponding monoacetal **6b** (39%) of 24% diastereomeric excess. Furthermore, reaction in the presence of (*S*,*S*)-cyclohexane-1,2-diol (3 equiv.) under the same reaction conditions afforded (−)-**5** (55%) of 56% e.e. as a sole product. The e.e. of **5** was determined by the ^{13}C NMR spectrum‡ after conversion into the corresponding bisacetal **7** using (*R*,*R*)-butane-2,3-diol under azeotropic conditions (*p*-TsOH, benzene).§ Next, the reaction conditions were studied with reference to the reaction temperature and equivalences of BF$_3$–Et$_2$O and (*S*,*S*)-cyclohexane-1,2-diol (Table 1). As shown in entries 1 and 2, an excess amount of BF$_3$-Et$_2$O did not afford satisfactory results. The ratio between BF$_3$–Et$_2$O and (*S*,*S*)-cyclohexane-1,2-diol affected both chemical and asymmetric yields. Furthermore, reaction at lower temperature gave better results in connection with the e.e. of (−)-**5** (entries 3–6), but reaction at −40 °C under similar conditions to entry 6 did not proceed at all. The best result was obtained by the following procedure (entry 6). To a solution of **3** (200 mg) and (*S*,*S*)-cyclohexane-1,2-diol (387 mg) in CH$_2$Cl$_2$, BF$_3$–Et$_2$O (0.28 ml) was added at 0 °C. The reaction mixture was stirred for 6 h at 0 °C. Usual work-up and purification by silica gel column chromatography afforded (−)-**5** (172 mg, 86%) of 85% e.e.¶,‖ This novel asymmetric induction might be caused by a chiral enol ether intermediate as a chiral enolate equivalent similar to the intermediate **D** in Scheme 2.

Table 1 Asymmetric spirocyclization



Entry	BF$_3$-Et$_2$O (equiv.)	Diol (equiv.)	*T*/°C	Yield (%)	% E.e.
1	7	1	Room temp. (4 h)	36	21
2	7	3	Room temp. (4 h)	55	56
3	1	1	Room temp. (4 h)	62	74
4	1	3	Room temp. (1.5 h)	83	70
5	1	1	0 (6 h)	23	81
6	1	3	0 (6 h)	86	85

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† *Selected spectroscopic data* for **5**: ^{1}H NMR (270 MHz, CDCl$_3$) δ 2.20–2.34 (8H, m), 1.58–1.97 (8H, m). ^{13}C NMR (25.05 MHz, CDCl$_3$) δ 209.8 (s), 53.0 (t), 43.5 (s), 40.8 (t), 34.2 (t), 21.4 (t). MS *m/z* 180 (M$^+$), 137, 123, 110. The ^{13}C NMR spectroscopic data agreed with those in ref. 3*a*.

‡ The d.e. of **7** could not be determined by ^{1}H NMR (270 MHz, CDCl$_3$) even in the presence of a shift reagent [Eu(fod)$_3$].

§ In this reaction, no decrease of e.e. was confirmed by repeating acetalization and deacetalization (5% aqueous HCl, Et$_2$O, room temp.), which suggests that asymmetric spirocyclization proceeded in an irreversible manner.

¶ The reaction in the case of using (*R*,*R*)-cyclohexane-1,2-diol afforded (+)-**5** (83%) of 85% e.e.

‖ (−)-**5** of 85% e.e. Colourless oil. $[\alpha]_D^{20}$ −14.3 (*c* 2.1, CHCl$_3$). *Selected spectroscopic data* of **7** derived from (−)-**5**: ^{1}H NMR (270 MHz, CDCl$_3$) δ 3.49–3.68 (4H, m), 1.25–1.95 (16H, m), 1.21–1.23 (12H, m). ^{13}C NMR (25.05 MHz, CDCl$_3$) δ 108.8 (s), 77.7 (77.9) (d), 44.9 (47.3) (t), 38.4 (35.9) (t), 37.4 (37.2) (t), 36.4 (36.7) (s), 19.3 (19.6) (t), 17.1 (16.9) (q). Chemical shifts in parentheses are those of the minor diastereoisomer. The absolute configuration of (−)-**5** is now under investigation, and further studies are underway on the asymmetric reaction based on this new concept.