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Flow Synthesis of (3*R*)- and (3*S*)-(*E*)-1-Iodohexa-1,5-dien-3-ol: Chiral Building Blocks for Natural Product Synthesis

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A concise procedure to prepare optically active (3*R*)- and (3*S*)-(*E*)-1-iodohexa-1,5-dien-3-ol was developed. Ethyl (*E*)-3-iodoacrylate was converted to racemic (*E*)-1-iodohexa-1,5-dien-3-ol under flow and batch conditions via successive half reduction followed by Grignard reaction. Kinetic resolution of the racemic alcohol was achieved under flow conditions by using lipase packed in a column to afford (3*S*)-(*E*)-1-iodohexa-1,5-dien-3-ol and corresponding (3*R*)-acetate. Removal of the acetyl group was also carried out under flow conditions by using ion exchange resin packed in a column and (3*R*)-(*E*)-1-iodohexa-1,5-dien-3-ol was obtained after simple evaporation of the eluent.

Optically active (3*R*)- and (3*S*)-(*E*)-1-iodohexa-1,5-dien-3-ol ((*R*)-**1** and (*S*)-**1**) are useful chiral building blocks for the synthesis of natural products (Figure 1).[1-4] During the course of our synthetic studies of amphidinol 3,[5] we have reported a concise synthesis of (*R*)-**1** and (*S*)-**1** via kinetic resolution of racemic alcohol *dl*-**1**.[5a]

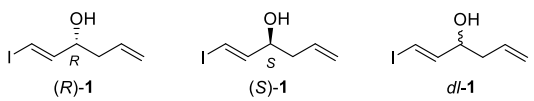
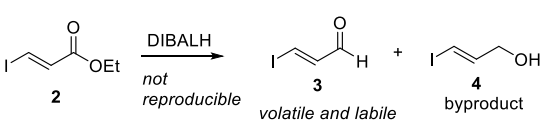


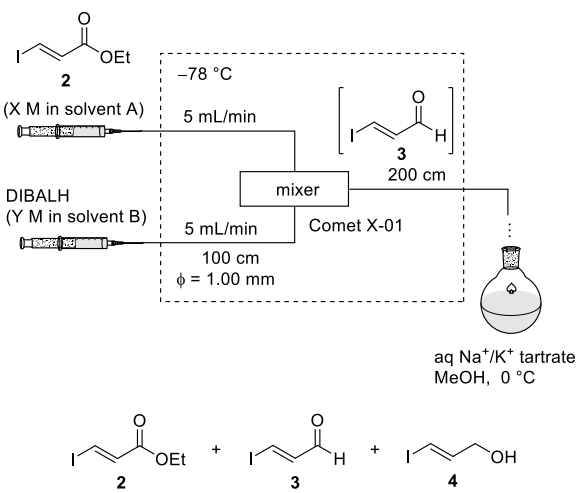
Figure 1. Structure of (3*R*)- and (3*S*)-(*E*)-1-iodohexa-1,5-dien-5-ol ((*R*)-**1** and (*S*)-**1**), and the corresponding racemic alcohol (*dl*-**1**).

Although *dl*-**1** was synthesized via Grignard reaction of aldehyde **3** with allylmagnesium bromide, half reduction of ester **2** with DIBALH giving aldehyde **3** was not reproducible (34-83%) with concomitant formation of byproduct **4** and recovery of **2**, and handling of **3** was difficult because of the volatile and labile property (Scheme 1). Herein, we report practical procedure for synthesizing *dl*-**1** by using microflow reactors,[6] and concise preparation of (*R*)-**1** and (*S*)-**1** under flow conditions.



Scheme 1. Unsuccessful half reduction of ester **2** with DIBALH under the batch conditions.

It is reported that half reduction of esters was successfully achieved by using microflow reactor by Eisai[7] and Jamison[8] group, therefore, we applied the method to our system (Scheme 2). A solution of **2** in solvent A and a solution of DIBALH in solvent B were transferred (tube length = 100 cm) and mixed through a microflow reactor (Comet X-01)[9] at a rate for 5.0 mL/min at −78 °C, and after passing through the tube (tube length = 200 cm), the reaction mixture was poured into a mixture of Et_2O and aqueous solution of Rochellet salt at 0 °C.



Scheme 2. Half reduction of ester **2** with DIBALH under flow conditions.

As shown in Table 1, mixing a solution of **2** in toluene (0.20 M) with a solution of DIBALH in toluene (0.24 M) resulted in the formation of aldehyde **3** with concomitant formation of alcohol **4** in a 63 : 37 ratio without recovery of **2** as determined by ^{1}H NMR analysis (entry 1). When the solvent was changed to CH_2Cl_2 (entry 2), the ratio of **3** was dramatically improved (**3** : **4** : **2** = 93 : 4 : 3). It is postulated that DIBALH forms dimer in less polar solvent such as hexane, but dissociation of the dimer occurred in CH_2Cl_2. Therefore, reactivity of DIBALH in CH_2Cl_2 was higher than that in hexane.

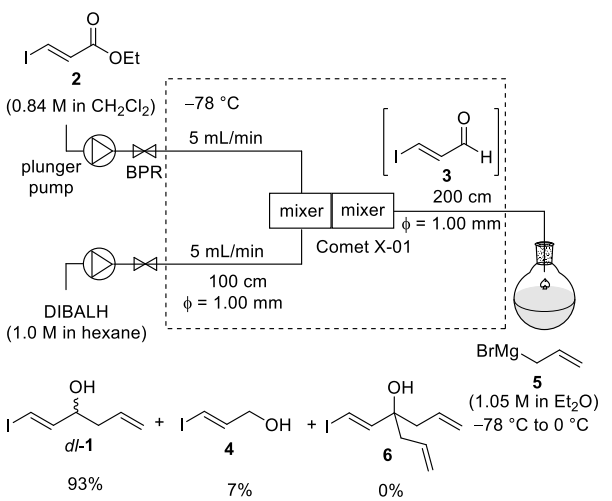
Table 1. Half reduction of **2** with DIBALH under the flow conditions.

entry	solvent A / X M	solvent B / Y M	ratio / %[a] **3** : **4** : **2**
1	toluene / 0.20	toluene / 0.24	63 : 37 : 0
2	CH_2Cl_2 / 0.20	CH_2Cl_2 / 0.24	93 : 4 : 3
3	hexane / 0.50	hexane / 0.70	88 : 12 : 0
4	CH_2Cl_2 / 0.84	hexane / 1.0	73 : 6 : 21
5[b]	CH_2Cl_2 / 0.84	hexane / 1.0	93 : 7 : 0
6[b]	CH_2Cl_2 / 1.0	hexane / 1.0	78 : 14 : 8

[a]The ratio was determined by ^{1}H NMR analysis. [b]Two micromixers were directly connected in series.

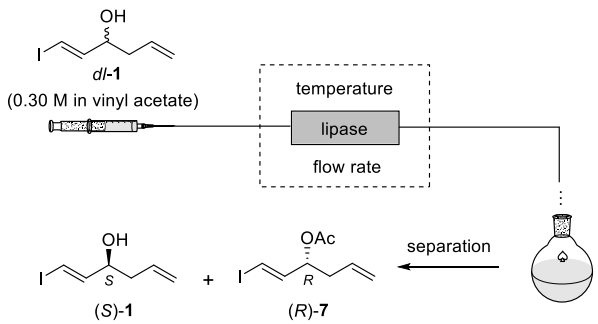
However, price of the DIBALH solution in CH_2Cl_2 is three times expensive than that in toluene or hexane. Therefore, hexane solution was used, and concentration of **2** and DIBALH was increased to 0.50 M and 0.70 M, respectively, aiming for the large scale synthesis (entry 3). As a result, acceptable ratio of **3** was obtained (**3** : **4** = 88 : 12). Next, we planned to use the commercially available 1.0 M DIBALH solution in hexane directly, and solvent for **2** was changed to CH_2Cl_2 (0.84 M) to increase the solubility at low temperature (entry 4). However, the considerable amount of **2** remained (**3** : **4** : **2** = 73 : 6 : 21). Although attempts to improve the ratio of **3** by prolong the resident time were unsuccessful, we found that direct connection of two micromixers in series was effective to result in the formation of **3** in high selectivity (**3** : **4** = 93 : 7, entry 5). In this reaction, mixing of the substrate and reagent is very important. Only one micromixer is not enough to complete the mixing of them. When the concentration of **2** was increased to 1.0 M, the yield of **3** was decreased (**3** : **4** : **2** = 78 : 14 : 8). Therefore, we decided that conditions in entry 5 was most suitable.

Having succeeded in the half reduction of **2**, synthesis of *dl*-**1** was examined without isolation of the aldehyde **3**. Although one flow synthesis was examined by mixing the solution of **3** with allylmagnesium bromide, the low solubility of the resulting alkoxide under the reaction conditions was problematic to cause choking the flow system. Therefore, flow and batch conditions were applied as shown in Scheme 3 for large scale synthesis. The half reduction of **2** (70.2 g) was carried out under the optimized conditions by using two microflow reactors in series (Table 1, entry 5), and plunger pumps were used for feeding the solutions. The resulting reaction mixture was poured into a solution of allylmagnesium bromide **5** in Et_2O (1.05 M) at −78 °C. After completing the flow reaction, the resulting reaction mixture was allowed to warm up to 0 °C to afford *dl*-**1** in 93% (64.9 g) yield with concomitant formation of small amount of **4** (7%) without byproduct **6**.



Scheme 3. Sequential DIBALH reduction of **2** under flow conditions and Grignard reaction with **5** under batch conditions without isolation of aldehyde **3**. BPR: back pressure regulator.

Having *dl*-**1** in hand, lipase catalyzed kinetic resolution under flow conditions was examined.[10] The advantages of using flow system with solid catalyst are as follows: 1) it is easy to recover and reuse the catalyst, 2) reaction time can be shortened because of higher catalyst/substrate ratio, and 3) once the reaction conditions are optimized, optical resolution can be performed continuously and reproducibly. After prescreening of lipases, CALB was selected and packed in a column and a solution of *dl*-**1** in vinyl acetate was eluted (Scheme 4).



Scheme 4. Lipase catalyzed kinetic resolution of *dl*-**1** under flow conditions.

As shown in Table 2, 0.68 g of lipase (CALB) was packed in a column (ϕ5 mm × 10 mm), and a solution of *dl*-**1** in vinyl acetate (0.30 M) was eluted at a rate of 10 mL/h at 50 °C (entry 1). The ratio of the resulting (*S*)-**1** and (*R*)-**7** was determined by ^{1}H-NMR analysis to be 51 : 49 and enantiomeric excess was determined by HPLC analysis using chiral column to be 91.0%ee and 90.0%ee, respectively. Next, the reaction was carried out at 60 °C, and the ratio of (*S*)-**1** : (*R*)-**7** was 44 : 56 in 96.8%ee and 74.5%ee, respectively (entry 2). When the flow rate was increased to 12 mL/h at 60 °C, the ratio of (*S*)-**1** : (*R*)-**7** was 45 : 55 in 97.2%ee and 80.4%ee, respectively (entry 3).

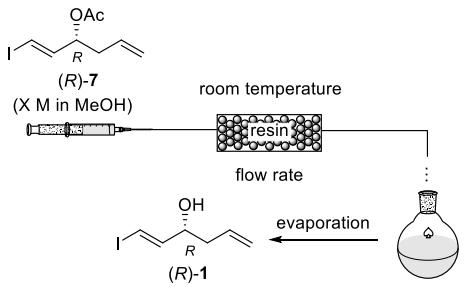
Table 2. Lipase catalyzed kinetic resolution of *dl*-**1**.[a]

entry	flow rate / mL/h	temp / °C	ratio / %[b] (*S*)-**1** : (*R*)-**7**	ee%[c] (*S*)-**1**	(*R*)-**7**
1	10	50	51 : 49	91.0	90.0
2	10	60	44 : 56	96.8	74.5
3	12	60	45 : 55	97.2	80.4

[a]A column of ϕ5 mm × 10 mm was used. [b]The ratio was determined by ^{1}H NMR analysis (600 MHz). [c]The enantiomeric excess was determined by HPLC analysis using Chiralpak AD, ϕ4.6 ×250 mm, 0.3% 2-propanol in hexane, 1.0 mL/min, 254 nm.

The final step of the synthesis is removal of the acetyl group of (*R*)-**7**, which was also carried out under flow conditions. Although removal of acetates are usually carried out under batch conditions by using K_2CO_3 in methanol, quenching, extraction, and evaporation sequence is required after the reaction. We planned to apply flow chemistry for this purpose by using anion exchange resin as a base

catalyst.[11] The advantage is the simple operation, i.e. only evaporation of the solvent is required for isolation of the product if the starting material is consumed completely. As shown in Scheme 5, a solution of the acetate (*R*)-**7** in methanol was passed through ion-exchange resin (DOWEX 1×4 50-100 Mesh) packed in a column (ϕ5 mm × 10 mm), which was washed with water, 1.0 M NaOH, water, and methanol prior to use (conversion of Cl^- form to MeO^- form).



Scheme 5. Removal of acetyl group of (*R*)-**7** under flow conditions with ion-exchange resin packed in a column.

As shown in Table 3, (*R*)-**7** in methanol (0.1 M) was passed through the resin (4.0 g) packed in a column (ϕ5 mm × 10 mm) at a flow rate of 0.5 mL/min (entry 1). As a result, methanolysis of (*R*)-**7** completely occurred to afford (*R*)-**1** as a single product after simple evaporation of the eluent (entry 1). When the concentration of the solution was increased to 0.5 M, the ratio of (*R*)-**1** and (*R*)-**7** was 91 : 9 (entry 2). Therefore, the flow rate was decreased to 0.3 mL/min to afford (*R*)-**1** as a single product (entry 3). The resin packed in the column can be reused as shown in entries 4 and 5. The present procedure would be useful for the water soluble polar products such as sugar derivatives, because simple evaporation is enough for isolation and no need of purification.

Table 3. Removal of the acetyl group of (*R*)-**7** under flow conditions. [a]

entry	conc of (*R*)-**7** / M	flow rate / mL/min	ratio / %[b] (*R*)-**1** : (*R*)-**7**
1	0.1	0.5	>99 : <1
2	0.5	0.5	91 : 9
3	0.5	0.3	>99 : <1
4[c]	0.5	0.3	>99 : <1
5[d]	0.5	0.3	>99 : <1

[a]A column of ϕ5 mm × 10 mm was used. [b]The ratio was determined by ^{1}H NMR analysis (600 MHz). [c]The column used in entry 3 was reused. [d]The column used in entry 4 was reused.

In conclusion, optically active (3*R*)- and (3*S*)-(*E*)-1-iodohexa-1,5-dien-3-ol was synthesized under flow conditions. Ethyl (*E*)-3-iodoacrylate was converted to racemic (*E*)-1-iodohexa-1,5-dien-3-ol under flow and batch conditions via successive half reduction with DIBALH followed by Grignard reaction. Kinetic resolution of the racemic alcohol with lipase was achieved under flow conditions to give (3*S*)-(*E*)-1-iodohexa-1,5-dien-3-ol and corresponding (3*R*)-acetate. Removal of the acetyl group was also carried out under flow conditions with ion exchange resin packed in a column and (3*S*)-(*E*)-1-iodohexa-1,5-dien-3-ol was obtained after simple evaporation of the solvent.

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Supporting Information is available on http://dx.doi.org/10.1246/cl.******.

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