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Original article

Non-superimposable mirror image crystals of enantiomers by spontaneous resolution and the chiral discrimination mechanism

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ABSTRACT

Non-superimposable mirror image crystals of both enantiomers (*S*/*R*) of cyclic γ-alkenyl alcohol (**2**) have been recognized and remarkably identified by the naked eye. More interestingly, both crystals are an outcome of most astonishingly H-bond and intermolecular $\sigma/\pi-\pi$ interactions. They accounted for the relatively rare and less predictable spontaneous resolution with optical purity >99% *ee* from the racemic mixture. The chiral discrimination mechanism of this spontaneous resolution has also been proposed.

1. Introduction

Asymmetric synthesis and chiral resolution are the two major tactics to achieve desired chiral compounds [1]. Both strategies always involve the use of discrete enantiomers, except with spontaneous resolution [2]. However, this phenomenon is very rare, poorly documented [3] and generally involves tedious preferential crystallization [4]. Homochiral crystallization is the simplest way to prepare enantiomers directly from the racemic mixture [5]. Should spontaneous resolution happen, it is a more convenient and economical approach [6], receiving huge interest. However, it is less predictable as the conglomeration processes have not yet been explored comprehensively [7]. It is well-known that supramolecular interactions, such as hydrogen bonding and coordination bonding have specific directions that can sometimes effectively transmit stereochemical information between adjacent homochiral molecules and play an imperative role in spontaneous resolution [8]. In 1848, Louis Pasteur, discovered the first, simplest separation of enantiomers by homochiral crystallization of a conglomerate. Two crystals were visually distinctive as hemihedral forms [9] and this uncommon and rare wonder was selected as one of the most memorable discoveries in chemistry by readers [10]. A few years ago, Lahav described a method for the direct determination of absolute configuration of chiral polar crystals based on the changes in crystal habit induced by tailor-made impurities [11]. In the history of chemistry and after the historic achievement of Pasteur, it seems miraculous that, herein, the recognition by the naked eye of both enantiomers (*S*,*R*) of cyclic γ-alkenyl alcohol (**2**) from solution and separation on the basis of physical appearance as a mirror image, has been achieved.

2. Experimental

We have targeted the chiral center at C-1′ position of cyclic γ-alkenyl ester **1** and alcohol **2** because of its importance in the syntheses of enantiopure octahydrobenzofuran derivatives. In this regard, the racemic **2** was synthesized (Scheme 1) using the literature procedure with modifications [12].

2.1. Methyl 2-(cyclohex-2-enyl)-2,2-diphenylacetate (1)

Lithium di-isopropylamide (LDA) was generated *in situ* by slow addition of *n*-BuLi (1.65 mL, 1.6 mol/L, 2.65 mmol, 1.3 equiv.) to the solution of di-isopropylamine (371 mg, 2.87 mmol, 1.2 equiv.) in THF (4 mL) and stirred for 0.5 h at −78 °C. Methyl diphenylacetate (500 mg, 2.21 mmol) in THF (5 mL) was added slowly over 1 h at the same temperature and stirred for an additional 1 h. 3-Bromocyclohexene (391.3 mg, 2.431 mmol, 1.1 equiv.) was added slowly to the reaction mixture, allowed to warm up at room temperature freely and stirred for 24 h. Quenched with aqueous HCl (5 mL, 1 mol/L), stirred and partitioned between H_2O (10 mL) and CH_2Cl_2 (3 ×20 mL), the organic layer was combined, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure and purified by column chromatography with EtOAc/*n*-hexane (1/20, v/v) afforded **1** as a clear colorless oil (500 mg, 86%) which was crystallized from *n*-hexane. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.26 (m, 10 H, 2Ph-H), 5.67–5.62 (m, 2H, 2′,3′-H), 3.81 (m, 1H, 2-H), 3.62 (s, 3H, Me), 1.88–1.01 (m, 6H, 4′,5′,6′-H).

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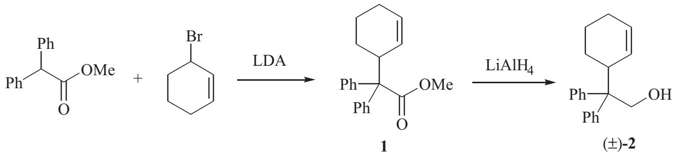


Scheme 1. Synthetic route of alcohol **2**.

2.2. 2-(Cyclohex-2-enyl)-2,2-diphenylethanol (2)

The solution of methyl ester **1** (891 mg, 2.30 mmol) in THF (15 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (122 mg, 3.22 mmol, 1.4 equiv.) in THF (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 24 h. Quenched with NaOH (3 mL, 1 mol/L) and H_2O (5 mL) at 0 °C, the suspension was filtered through celite and washed with Et_2O (30 mL). The filtrate and organic layer were combined, dried over anhydrous Na_2SO_4, filtered, concentrated under reduced pressure, and purified by column chromatography. The elution of 4% EtOAc in *n*-hexane afforded **2** as a white solid (500 mg, 86%), mp 126–128 °C (from *n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23–7.21 (m, 10H, 2Ph-H), 5.81 (d, 1H, J = 10.4 Hz, 2′-H), 5.68–5.64 (m, 1H, 3′-H), 4.2 (s, 2H, 1-H), 3.3–3.2 (m, 1H, 1′-H), 1.9–1.0 (m, 6H, 4′,5′,6′-H). Resolution was accomplished and both enantiomers were recognized by chiral HPLC on Chiralpak AD-H (*n*-hexane/*i*-propanol = 99.9/0.1, v/v, 1.0 mL/min, 254 nm), t_S = 16.9 min, t_R = 18.3 min; $[\alpha]_D^{28}$ −1.9 (*c* 0.254, CH_2Cl_2, for (*S*)-**2**), $[\alpha]_D^{28}$ +1.6 (*c* 0.254, CH_2Cl_2, for (*R*)-**2**).

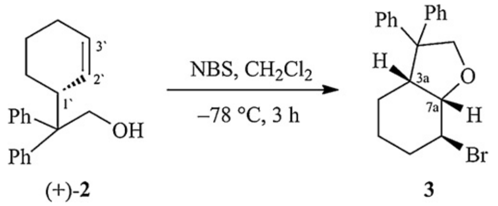
2.3. 7-Bromo-3,3-diphenyl-octahydrobenzofuran (3)

N-Bromosuccinimide (NBS, 10.5 mg, 0.06 mmol, 1.2 equiv.) was added to the solution of alcohol (+)-**2** (13.9 mg, 0.05 mmol, 1.2 equiv.) in CH_2Cl_2 (0.5 mL) at −78 °C (Scheme 2). The reaction mixture was stirred at −78 °C for 2.5 h. Upon completion as monitored by thin layer chromatography, the crude product was directly loaded on column and purified by flash silica gel column chromatography (Et_2O/petroleum ether (1/40, v/v) afforded **3**, white crystals (15 mg, 84%). Mp 87–89 °C (from *n*-Hexane), ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.37 (d, 2H, J = 7.5 Hz, Ph), 7.29 (d, 2H, J = 7.5 Hz, Ph), 7.27–7.23 (m, 2H, Ph), 7.17–7.13 (m, 4H, Ph), 4.73 (d, 1H, J = 8.2 Hz, 2-H_a), 4.65 (d, 1H, J = 8.2 Hz, 2-H_b), 4.42 (t, 1H, J = 4.1 Hz, 7-H), 4.38 (dd, 1H, J = 7.5 Hz, 4.14 Hz, 7a-H), 3.31–3.27 (m, 1H, 3a-H), 1.95–1.93 (m, 1H, 6a-H), 1.89–1.88 (m, 1H, 6b-H), 1.73–1.69 (m, 2H, 5-H), 1.32–1.29 (m, 1H, 4a-H), 1.14–1.12 (m, 1H, 4b-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.7, 143.3, 128.8, 128.4, 128.2, 126.8, 126.5, 126.3, 81.2, 76.1, 58.8, 52.3, 41.5, 29.4, 24.9, 19.7. HRMS calcd. for $C_{20}H_{21}BrO$: 379.0668 $[M+Na]^+$, found: 379.0678. $[\alpha]_D^{28}$ +133 (*c* 0.218, CH_2Cl_2 for (3a*R*,7a*S*,7*S*)-**3**).

3. Results and discussion

3.1. The spontaneous resolution

Through free evaporation of the standing solution of **2** (700 mg) in mixed ethyl acetate and *n*-hexane (50 mL, 1:40, v/v) at 25 °C, spontaneous resolution occurred and yielded bona fide crystal flowers. Upon further scrutinizing, each crystal flower consisted of numerous well defined crystal petals with purity ranging from 50% *ee* to 89% *ee* (Fig. 1, Step 1). Thus, these crystal petals were separated and used as seed crystals in the subsequent preferential crystallization (Fig. 1, Step 2). With these rectangular shape crystal seeds, more crystal flowers were grown with the same absolute configuration as the seed from a hot (50 °C), diluted solution of racemic **2** in *n*-hexane (resolution efficiency [13], *E* = 45.9). The crystals of the other enantiomer were obtained either from mother liquor (*E* = 84.3), or by the same procedure, using seed crystals with the opposite handedness (Fig. 1, Step 2). Further, simple recrystallization (Fig. 1, Step 3) was carried out 2 or 3 times leading to successful resolution of both enantiomers of **2** in >99.9% *ee*. The absolute configuration was established based on the single crystal of halogenation derivative (+)-(3a*R*,7a*S*,7*S*)-**3** (Scheme 2) [14].



Scheme 2. Synthetic route of **3**.

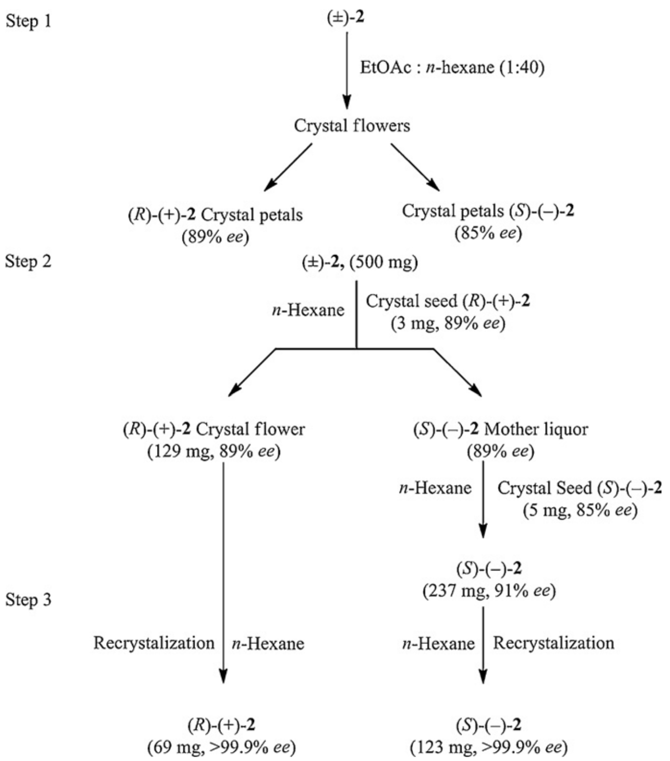


Fig. 1. Resolution of (±)-**2**. Step 1: spontaneous resolution; Step 2: preferential crystallization; and Step 3: simple recrystallization.

Scrutinizing the crystal flowers provided a foundation to develop a highly efficient and clean spontaneous resolution. Further optimization was attempted to get pure crystals or crystal flowers of each enantiomer by spontaneous resolution directly from a racemic solution. Low temperature (−15 °C) gave the crystal of low purity. Interestingly, by changing the volume and polarity of the solvent, slow crystallization affected the ratio of crystals and crystal flowers, as well as the size and optical purity (see Table S1 in Supporting information,). Finally, after great laborious work, crystal flowers consisting of well-defined crystal petals of each enantiomer were separated with a purity >99% *ee* from the solution of **2** (300 mg) consisting of a mixture of EtOAc/*n*-hexane (33 mL, 1/10, v/v) (Fig. 2). All these crystals were identified by the naked eye (*S*/*R*) and were separated on the basis of physical appearance as a mirror image (Fig. 3, also see Fig. S2 in Supporting information).