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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 σ/π–π 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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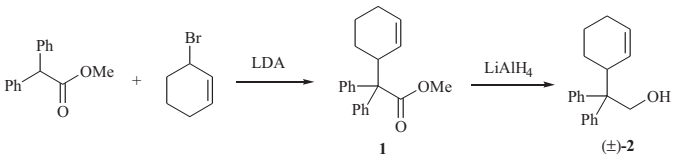


Scheme 1. Synthetic route of alcohol **2**.

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**).

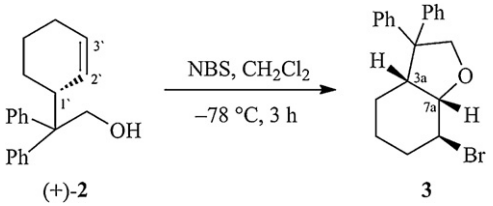
2.3. 7-Bromo-3,3-diphenyl-octahydrobenzofuran (**3**)

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,



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

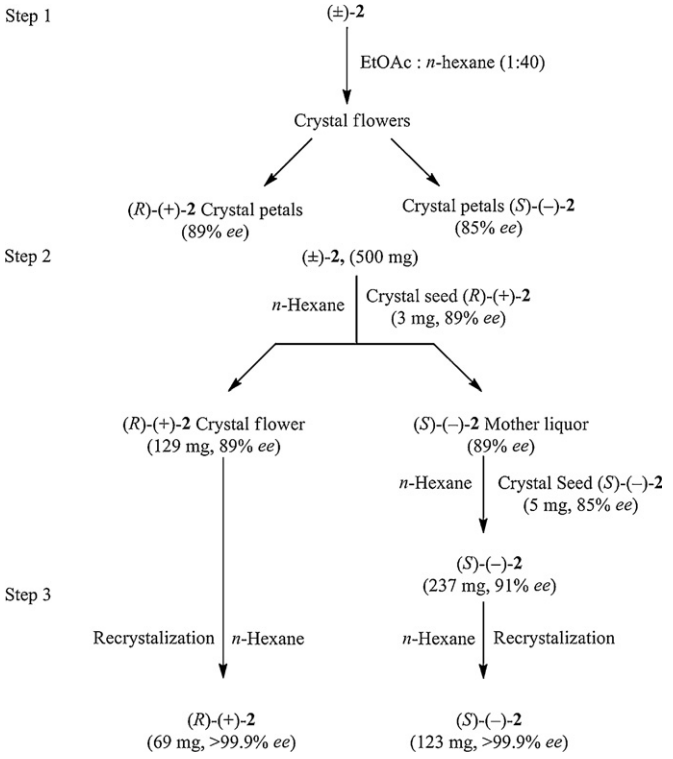


Fig. 1. Resolution of (±)-**2**. Step 1: spontaneous resolution; Step 2: preferential crystallization; and Step 3: simple recrystallization.

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].

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).

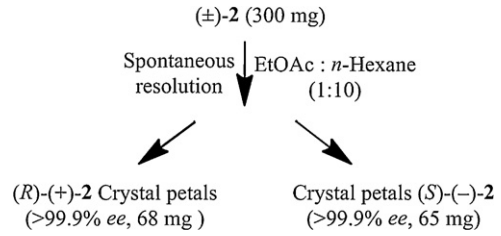


Fig. 2. Graphic representation of spontaneous resolution of (±)-**2**.

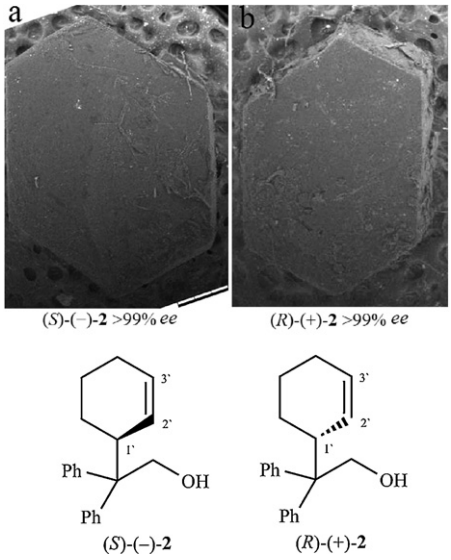


Fig. 3. SEM mirror images and structure of **2**. (a) (*S*)-(−)-**2** and (b) (*R*)-(+)-**2**.

3.2. The mechanism of the spontaneous resolution

Once a clean spontaneous resolution procedure was established, which interestingly led to non-superimposable mirror image crystals, the discrimination mechanism of this spontaneous resolution was elucidated by the non-covalent interactions during the crystallization. As we know, the characteristics of solid-state materials are inherently linked to the order in which the atoms are arranged [15]. During crystallization, molecules are arranged in an orderly manner and packed as tightly as possible through H-bond network, π–π stacking, van der Waals interaction, and supramolecular packing mode to realize the minimum energy in the crystal lattice [16]. These numerous weak intermolecular interactions between homo- and hetero-chiral enantiomers are important for chiral resolution. The good quality single crystal of (−)-**2** was obtained from *n*-hexane for X-ray single crystallographic analysis [17]. The colorless, hexagonal crystal belongs to the monoclinic space group P2(1) and the unit cell contains two molecules (Fig. 4). Crystallographic lattice parameters of all related compounds are summarized in Table 1. Scrutiny of these single crystal data helps us to elucidate the mechanism of this spontaneous resolution.

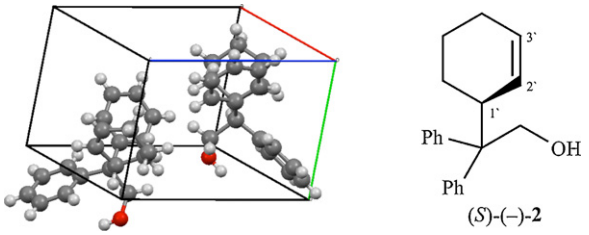


Fig. 4. Molecular packing in unit cell of (−)-**2**.

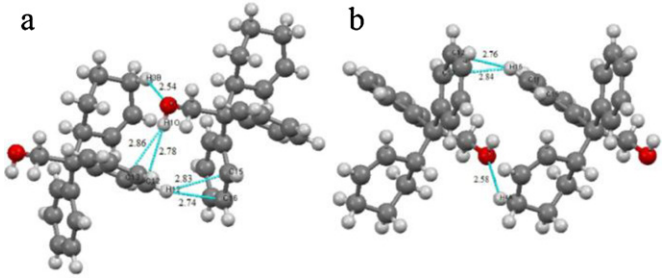


Fig. 5. σ/π–π and allylic H-bond interactions. (a) (−)-**2** and (b) (+)-**2**.

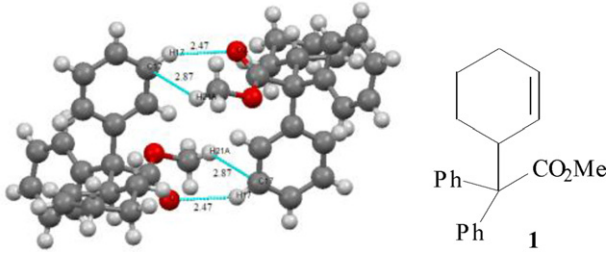


Fig. 6. σ–π and H-bond interactions in **1**.

First, π–π stacking and special hydrogen bonds are recognized, in the chiral discrimination [18] and for growth of both (−)-**2** and (+)-**2** single crystals. The distance of about 7.65 Å clearly demonstrates the absence of ordinary hydrogen bonds between

Table 1
Single crystal structure data of (±)-**1**, (−)-**2** and (+)-**2**.

	(−)-**2**	(+)-**2**	(±)-**1**
Empirical formula	$C_{20}H_{22}O$	$C_{20}H_{22}O$	$C_{21}H_{22}O_2$
Formula weight	278.38	278.38	306.39
Temperature	153(2) K	143(2) K	153 (2) K
Wavelength	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system, space group	Monoclinic, P2(1)	Monoclinic, (1)	Triclinic, P-1
Unit cell dimensions	a = 8.947(2) Å, alpha = 90° b = 7.1033(19) Å, beta = 95.199(4)° c = 11.670(3) Å, gamma = 90°	a = 8.981(3) Å, alpha = 90° b = 7.106(2) Å, beta = 95.604(5)° c = 11.773(4) Å, gamma = 90°	a = 8.866(3) Å, alpha = 96.248(2)° b = 9.638(3) Å, beta = 102.875(4)° c = 11.666(4) Å, gamma = 116.890(4)°
Volume	738.6(3) $Å^3$	747.7(4 $Å^3$	841.2(5) $Å^3$
Z, calculated density	2, 1.252 Mg/m^3	2, 1.236 Mg/m^3	2, 1.210 Mg/m^3
Absorption coefficient	0.075 mm^{-1}	0.074 mm^{-1}	0.076 mm^{-1}
Crystal size	0.40 × 0.38 × 0.36 mm	0.19 × 0.19 × 0.16 mm	0.40 × 0.39 × 0.35 mm
Reflections collected/unique	7328/2611 [R(int) = 0.0251]	6325/2145 [R(int) = 0.0316]	9589/3808 [R(int) = 0.0261]
Completeness to theta	31.50 99.0%	29.15 98.6%	27.50 98.4%
Final R indices [$I > 2$ sigma (I)]	$R1$ = 0.0357, w$R2$ = 0.0853	$R1$ = 0.0545, w$R2$ = 0.1275	$R1$ = 0.0591, w$R2$ = 0.1417
R indices (all data)	$R1$ = 0.0375, w$R2$ = 0.0865	$R1$ = 0.0684, w$R2$ = 0.1383	$R1$ = 0.0777, w$R2$ = 0.1549

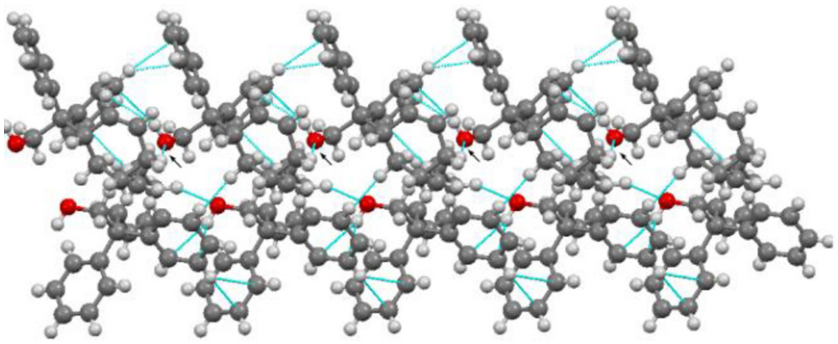


Fig. 7. σ/π–π and H-bond interactions between and within layers in (−)-**2**.

free OH groups. Contrary to our anticipation, in the single crystal of (−)-**2** (Fig. 5a), hydrogen (H10) of the hydroxyl group in one molecule has strong interaction with π electrons of two carbons (C12 and C13) of the phenyl ring of the neighboring molecule at a distance of 2.78 Å and 2.86 Å, respectively, which is not observed in the single crystal of (+)-**2** (Fig. 5b). And in turn, the phenyl ring *via* hydrogen (H12) of the latter molecule shows vertical π–π interaction with the phenyl ring of the former molecule (C15 and C16) at a distance ranging from 2.83 Å to 2.74 Å (Fig. 5). Most astonishingly, oxygen (O1) of the OH group exerts a strong connection with allylic hydrogen (H3b) at a distance ranging from 2.54 Å to 2.58 Å.

Comparing with **2**, spontaneous resolution of its precursor methyl ester **1** failed under the same conditions, but yielded crystal aggregates or crystals with optical purity about 2% *ee* or 4% *ee*. Closely examining the single crystal structure of (±)-**1** [17] reveals that lone electron pair of the carbonyl oxygen (O2) connects to the hydrogen (H17) attached to the phenyl ring of the opposite enantiomeric molecule at a distance of 2.47 Å, as well as the carbon (C17) to the hydrogen (H21) of methyl ester at a distance of 2.87 Å (Fig. 6). It indicates the directions of σ/π–π interactions and an uncommon H-bond involving allylic hydrogen (Fig. 5) and provides the reason of the spontaneous resolution of (±)-**2**.

Further, in the single crystal of (−)-**2**, layers of molecules are well stacked over each other and stabilized by vertical σ/π–π interaction [19]. In addition, as shown in Fig. 7, the series of layers are packed by an additional σ–π interaction between H5A and C10. Close observation of these layers indicates the benzene ring carbon (C10) has strong interaction with hydrogen C6′-H5A at a distance of 2.76 Å. Similarly the phenyl carbon of this molecule (C10) interacts with the sp^3 hydrogen H5A of another molecule and thus extends the stacked layers (Fig. 7). Consequently, the concerted σ–π interactions within layers and σ/π–π network between layers exist in the homochiral single crystal, which should be the most expected reason of this spontaneous resolution.

4. Conclusion

In conclusion, after the discovery of Pasteur, macro enantiomerically pure, non-superimposable mirror image crystals have been recognized and efficient spontaneous resolution has been established as a result of intermolecular σ/π–π stacking and allylic H-bond interaction. This investigation afforded not only a new example of spontaneous resolution, but also an excellent preparative route for the synthesis of chiral heterocycles without any external chiral sources.

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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.cclet.2013.04.045.

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