Tetrahedron Letters 58 (2017) 4491–4495

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Diastereomeric process-based chiral resolution of helical quinone derivatives using (−)-menthyl chloroformate

Mohammad Shahabuddin, Md. Sharif Hossain, Takao Kimura, Michinori Karikomi [*]

Department of Material and Environmental Chemistry, Graduate School of Engineering, Utsunomiya University, 7-1-2 Yoto, Utsunomiya, Tochigi 321-8585, Japan

ARTICLE INFO

Article history:
Received 26 August 2017
Revised 5 October 2017
Accepted 11 October 2017
Available online 12 October 2017

Keywords:
Helicenes
Bisphenols
Quinones
Chiral resolving agent
Circular dichroism

ABSTRACT

Diastereomeric resolution of helically distorted polycondensed bisphenols (1,1′-bibenzo[*c*]phenanthrene-2,2′-diols: HEBPOLs) **2a**–**b** was conducted utilizing (1*R*)-(−)-menthyl chloroformate as a chiral resolving agent. Subsequent manipulation produced highly optically pure [>99% enantiomeric excess (*ee*)] quinone derivatives (*P*) and (*M*)-**1a**–**b** in very good yields. The absolute configuration of each product was confirmed based on circular dichroism (CD) spectra and X-ray crystal structure analysis.

Introduction

Helicenes and helicene-like molecules are attracting much attention due to their unique screw-shaped and π-conjugated aromatic system consisting of *ortho*-condensed aromatic and/or hetero aromatic rings. As the number of *ortho*-annulated rings is increased, these molecules adopt a helical configuration to avoid collision of the terminal aromatic nuclei resulting in left- and right-handed chiral helical structures of (*P*) and (*M*) configurations, respectively.[1]

The extraordinary unique chiroptical properties of helicene and helicene-like molecules have initiated asymmetric synthetic approaches for applications in advanced organic materials including organic light emitting diode (OLED) materials[2] and organic field-effect transistors (OFET).[3] Several asymmetric synthetic approaches have been reported for the preparation of enantiomerically pure helicene-like molecules. However, most asymmetric synthesis reactions require substrates that are expensive or difficult to obtain.[4] Furthermore, this procedure generates optically active derivatives, however it rarely produces highly optically pure derivatives.[4c]

In our previous research, we described the asymmetric synthesis of helical quinone derivatives from 2-hydroxybenzo[*c*]phenanthrenes using copper-chiral amine complexes. The product yields were excellent but in terms of optical purity, the results were unsatisfactory. The exception was (*P*)-bromo-substituted quinone, where we obtained a 97% *ee*. The main disadvantages of this asymmetric synthesis process is low optical yields and limited applications for other substituted quinone derivatives.[5]

Menthyl chloroformate-mediated optical resolution of axially chiral bisphenols such as BINOL and related compounds has been reported.[6] However, compared to BINOL, HEBPOLs are sterically hindered substrates.[7] Thus, it is challenging to implement the same protocol for HEBPOLs. Here, we report a convenient and short experimental procedure for the optical resolution of quinone derivatives **1a**–**b**[8] with excellent *ee*. This method employs a diastereomeric process using (1*R*)-(−)-menthyl chloroformate as a chiral resolving reagent. Of course, BINOLs and HEBPOLs are completely resolved in each enantiomer by using chiral stationary phase columns. However, the diastereomeric process-based chiral resolution has advantage in the view point of cost and generality.

Results and discussion

Previously, we have shown the simplest way to synthesize HEBPOL derivatives.[7] After obtaining the HEBPOLs (*rac*)-**2a**–**c** from racemic quinone derivatives **1a**–**c**, we investigated their optical resolution. To perform this analysis, we examined the utility of commercial (1*R*)-(−)-menthyl chloroformate as a chiral resolving agent, which is used to convert HEBPOLs into their corresponding diastereomeric mixture of (S_a,*R*)-**3a**–**b** and (S_a,*R*)-**3a**–**b**. Thus, treatment of racemic HEBPOLs **2a**–**c** with (1*R*)-(−)-menthyl chloroformate (2.0 equiv), in the presence of triethylamine (Et_3N) in $CHCl_3$

---

[*] Corresponding author.
E-mail address: karikomi@cc.utsunomiya-u.ac.jp (M. Karikomi).

https://doi.org/10.1016/j.tetlet.2017.10.027
0040-4039/

at room temperature for 2–4 h, led to a 1:1 mixture (confirmed by ^{1}H NMR) of the two diastereomers, (S_a,R)-**3a**–**b** and (R_a,R)-**3a**–**b** (Scheme 1). The crude product was then purified by flash column chromatography using silica gel as a stationary phase and $CHCl_3$ as an eluent to obtain pure white solids of (S_a,R)-**3a**–**b** and (R_a,R)-**3a**–**b** in excellent yields (Scheme 1). Under the same reaction conditions, **2c** did not react to form diastereomers. Only unreacted **2c** was recovered. A possible explanation might be the presence of a methyl group at the *ortho*-position adjacent to the hydroxy group of **2c**. The *ortho*-methyl group may induce strong steric hindrance towards (1*R*)-(−)-menthyl chloroformate thus preventing the reaction. We also performed several modifications of the reaction conditions including increasing the following: reaction time, reagent ratios and reagent solvents. However, in every case, the results were unsuccessful. Even when we used two equimolar amounts of (1*R*)-(−)-menthyl chloroformate, in the cases of **2a** and **2b** only one hydroxyl group reacted. These results suggested that the HEBPOL hydroxy groups were already in a sterically hindered environment. Therefore, optical resolution using (1*R*)-(−)-menthyl chloroformate applied to HEBPOLs revealed its limited utility with a large sterically hindered substrate. However, to separate the diastereomers of **3a**–**b**, we first performed open column chromatography over a silica gel. Different solvent mixtures were tested, but none of them proved suitable. Subsequently, other attempts to separate these diastereomers by fractional crystallization in several solvent mixtures were also unsuccessful. However, the diastereomers were satisfactorily separated by ordinary phase HPLC (separation factor: $\alpha = 1.2$) using a Si60 column (φ 4.6 mm × 250 mm) under the following conditions: *n*-hexane/$CHCl_3$ (7:3 v/v) was utilized as the mobile phase, the flow rate was 1.0 ml/min, the temperature was 293 K and UV detection was performed at 254 nm. Next, we performed recycling preparative HPLC. The diastereomeric mixture (100 ± 5 mg) was eluted at room temperature on a Cica-MERCK Si60 HPLC column (φ 20 mm × 250 mm) with *n*-hexane/$CHCl_3$ (7:3 v/v) comprising the mobile phase with a flow rate of 3.8 ml/min.

The earlier eluting fraction (*F1*) contained (S_a,R)-**3a**–**b** that displayed a positive Cotton effect in the CD spectrum and also exhibited positive optical rotation values. After collecting the fractions and evaporation under reduced pressure, we obtained a 34% yield of (S_a,R)-**3a** and a 33% yield of (S_a,R)-**3b**. The later eluting fraction (*F2*) contained the second diastereomers (R_a,R)-**3a** and (R_a,R)-**3b** with a 44% yield and a 37% yield, respectively. Complete separation of diastereomers (% de) was determined by analytical HPLC and by comparative ^{1}H NMR spectra (Table 1 and Fig. 1). In the ^{1}H NMR spectra, the -OH proton displayed a characteristic signal at 6.10 ppm for the (S_a,R)-**3a** diastereomer and at 6.33 ppm for the (R_a,R)-**3a** diastereomer (Fig. 1). The specific optical rotation values obtained for (S_a,R)-**3a**–**b** and (R_a,R)-**3a**–**b** in the MeCN solution were high compare to the values of the related compound such as BINOL which shows around ±35 degree[9] (Table 2, entries 1–4). Subsequently, the resulting optically active diastereoisomers (S_a,R)-**3a**–**b** and (R_a,R)-**3a**–**b** were separately hydrolyzed at reflux in aqueous KOH/EtOH to generate each enantiomers of HEBPOLs (*S*)-**2a**–**b** and (*R*)-**2a**–**b**. Analogous experiments showed that the amount of water in the reaction system was very important for

Table 1

Diastereomer separation using preparative HPLC.

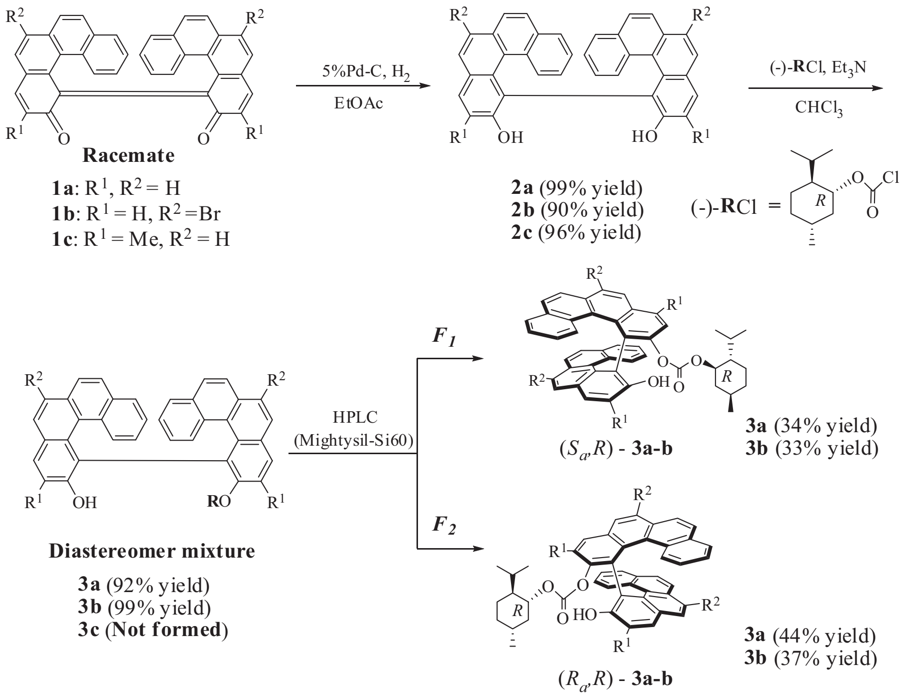
Entry	Compound[a]	% Yield[b]	t_R/min[c]	α[d]	% *de*[c]
1	(S_a,R)-**3a**	34	12.75	1.20	>99.5
2	(R_a,R)-**3a**	44	14.40		>99
3	(S_a,R)-**3b**	33	14.78	1.21	>99.5
4	(R_a,R)-**3b**	37	16.84		>99

[a] Recycling preparative HPLC column: Cica-MERCK Mightysil Si60® (φ 20 × 250 mm; 5 μm). Mobile phase: *n*-hexane/$CHCl_3$ (7/3); flow rate: 3.8 ml/min.

[b] Yields were calculated after separation.

[c] Analytical HPLC column: Cica-MERCK Mightysil Si60® (φ 4.6 × 250 mm; 5 μm). Mobile phase: *n*-hexane/$CHCl_3$ (7/3); flow rate: 0.8 ml/min.

[d] Separation factor, $\alpha = K_2/K_1$ were determined from analytical HPLC where Retention factor, $K_n = t_R - t_0/t_0$ and t_0 is the retention time of standard 1,3,5-tri-*tert*-butylbenzene (4.64 min).



Scheme 1. Synthesis and separation of diastereomers **3a**–**b**.