


 Cite this: *RSC Adv.*, 2022, 12, 8249

 Received 3rd March 2022  
Accepted 8th March 2022

DOI: 10.1039/d2ra01408d

[rsc.li/rsc-advances](https://rsc.li/rsc-advances)

# Asymmetric total synthesis of (1*S*,2*S*,4*S*)- $\beta$ -elemene†

 Wei Chen,<sup>ab</sup> Zhun Feng<sup>\*a</sup> and Qiang Liu<sup>\*b</sup>

Elemenes are sesquiterpene natural products extracted from Chinese medicinal herbs and have been used as an important antitumor drug in China. Here, we report the first stereoselective total synthesis of (1*S*,2*S*,4*S*)- $\beta$ -elemene using (*R*)-carvone as a chiral pool starting material. The isopropenyl moiety was achieved in a highly stereoselective manner through 1,4-Michael conjugate addition. The following transformations like regio- and stereoselective aldol condensation, Wittig olefination have been employed as the key steps, resulting in a concise total synthesis of (1*S*,2*S*,4*S*)- $\beta$ -elemene. Our accomplishment will allow further biological investigations of this natural product and open opportunities for developing a new potentially promising antitumor drug.

## Introduction

Traditional Chinese medicine (TCM) has been used to prevent and treat diseases for thousands of years, and now plays a more and more important role in the small molecule drug discovery.<sup>1</sup> One of the most significant and recent developments is the use of elemenes in the treatment of various malignant tumors.<sup>2</sup> Elemenes are a family of sesquiterpenes extracted from the Chinese medicinal herb *Curcuma Rhizoma*, and are classified into  $\alpha$ -elemene (A),  $\beta$ -elemene (B),  $\gamma$ -elemene (C),  $\delta$ -elemene (D) according to the position of the double bond (Fig. 1).<sup>3</sup> Owing to their extensive and potent *in vitro* and *in vivo* antitumor activities, elemene oral emulsion and elemene injection have been approved by the China National Medical Products Administration (NMPA) as noncytotoxic broad-spectrum antitumor drugs,<sup>2a,e</sup> and are currently under consideration for clinical studies in the United States.<sup>4</sup>

(1*S*,2*S*,4*R*)- $\beta$ -Elemene (**1**, Fig. 1) is the predominant active ingredient of clinically administrated elemene antitumor drugs, with a recommended content of not less than 85%.<sup>2e</sup> Previous studies have indicated that **1** not only inhibits the growth of tumor but also enhances the activity of immune system,<sup>5</sup> and even can reverse multiple-drug resistance,<sup>6</sup> making it unique to the conventional chemotherapeutic drugs. Interestingly, (1*R*,2*R*,4*S*)- $\beta$ -elemene (**2**), the enantiomer of **1**, was isolated from lower plants or microorganisms, such as the gorgonian *Eunicea mammosa*,<sup>7</sup> while **1** is commonly widespread in higher plants.

Very recently, a new isomer of  $\beta$ -elemene, namely (1*S*,2*S*,4*S*)- $\beta$ -elemene (**3**), was isolated and characterized by Shi and co-workers from the essential oil of *Curcuma wenyujin*.<sup>8</sup> As compared to **1**, **3** was found to possess higher antitumor activities for all cancer cell lines tested and lower toxicity in mice,<sup>8</sup> demonstrating its potential importance in the development of a new promising anticancer agent. However, the exceptionally low content of **3** in the Chinese medicinal herb greatly restricted its systematic pharmacological evaluation. Therefore, development of an efficient and practical approach to synthesize **3** using readily available reagents under mild reaction conditions is highly desirable.

The intriguing pharmacological properties and structural diversities of  $\beta$ -elemene have attracted significant attention from the synthetic community.<sup>9</sup> Indeed, several elegant

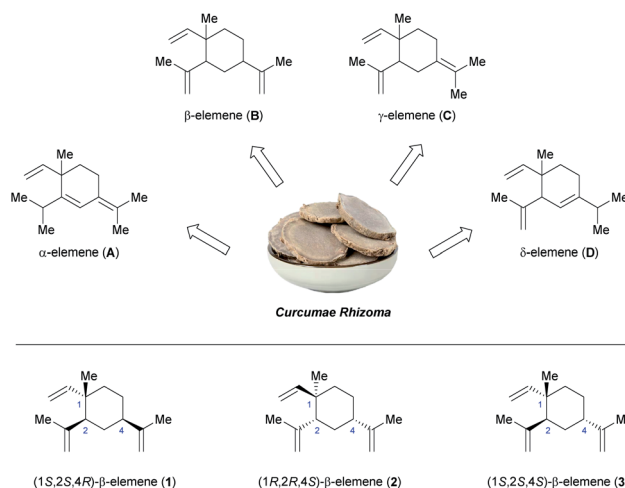


Fig. 1 Representative elemene sesquiterpenes.

<sup>a</sup>Guangdong-Macao Traditional Chinese Medicine Technology Industrial Park Development Co., Ltd., Zhuhai 519031, P. R. China. E-mail: zhun.feng@gmtcnpark.com

<sup>b</sup>School of Chinese Medicine, Southern Medicinal University, Guangzhou 510515, P. R. China. E-mail: gzlq2002@163.com

† Electronic supplementary information (ESI) available: copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra. See DOI: 10.1039/d2ra01408d

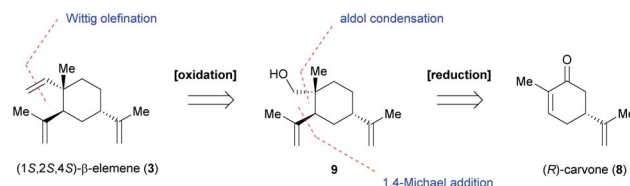


asymmetric total syntheses of  $\beta$ -elemene have been described in the literature or patents.<sup>4a,10–12</sup> In 1967, Rao and co-workers described the first asymmetric total synthesis of **1** in 9 steps using ozonolysis of  $\alpha$ -santonin **4** as the key transformation (Scheme 1a).<sup>10</sup> In 1995, Corey and co-workers reported the first asymmetric total synthesis of **2** in 7 steps *via* enantioselective Ireland-Claisen rearrangement of  $\beta,\gamma$ -unsaturated ester from geraniol **6** (Scheme 1b).<sup>11</sup> To the best of our knowledge, the total synthesis of (1*S*,2*S*,4*S*)- $\beta$ -elemene (**3**) has yet to be reported. Herein, we present the first and asymmetric total synthesis of **3** in five or eight steps from (*R*)-carvone **8**, a commercially available chiral pool starting material (Scheme 1c).

## Results and discussion

Intrigued by the fascinating pharmacological properties of (1*S*,2*S*,4*S*)- $\beta$ -elemene (**3**), we embarked on the first total synthesis of this sesquiterpene natural product. Our conceptual route to **3** is shown in Scheme 2. Retrosynthetically, **3** could be traced back to primary alcohol **9** *via* Wittig olefination and common oxidation reaction. We then envisioned that **9** could be generated from the chiral pool starting materials **8** by employing chemoselective and diastereoselective 1,4-Michael conjugate addition of Grignard reagent, aldol condensation and simple reduction of ketone.

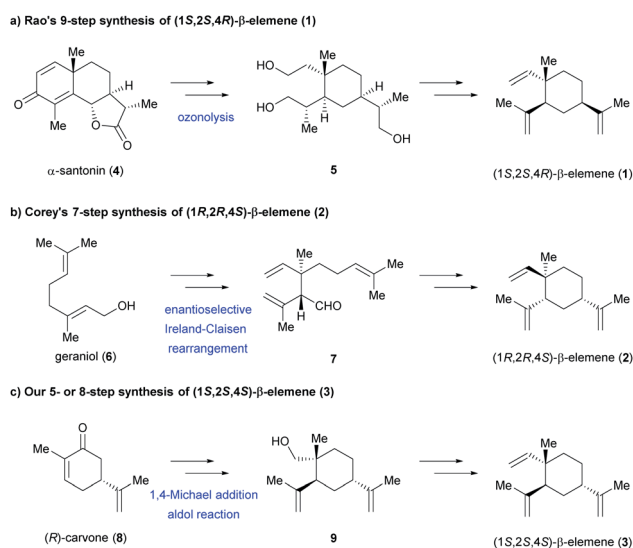
Chiral pool synthesis represents a useful approach to synthesize enantiopure organic molecules from readily available enantiomerically pure compounds, which features low cost, high abundance, and general renewability.<sup>13</sup> Therefore, our synthesis began with the preparation of optically pure intermediate **12** from the chiral pool building block (*R*)-carvone **8** (\$0.39 per g, Merck), as shown in Scheme 3. Stimulated by Knölker's pioneering work,<sup>14a</sup> it was anticipated that the new generated stereogenic center in cyclohexanone **11** could be secured by diastereoselective 1,4-Michael addition of isopropenyl Grignard reagent **10** to **8**.<sup>14b</sup> To our delight, we were



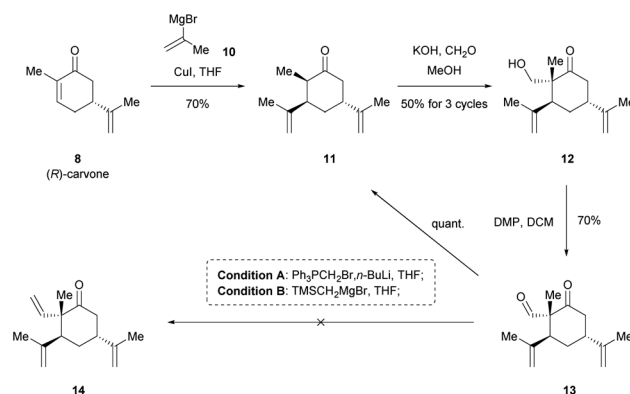
Scheme 2 Retrosynthetic analysis of (1*S*,2*S*,4*S*)- $\beta$ -elemene.

able to isolate desired product **11** exclusively in 70% yield. Notably, the steric and electronic influence in the diastereoselective transformations of chiral enolates have been systematically studied by Krause's group.<sup>15</sup> Treatment of **11** with formaldehyde in the presence of KOH afforded primary alcohol **12** as a single diastereomer in 50% isolated yield for three cycles.<sup>14b,16</sup> Subsequently, oxidation of **12** with Dess–Martin periodinane (DMP)<sup>17</sup> gave aldehyde **13** in 70% yield. In an attempt to obtain advanced intermediate **14** *via* Wittig olefination, several reaction conditions (*e.g.*,  $\text{PPh}_3\text{PCH}_2\text{Br}/n\text{-BuLi}$ ,  $\text{TMSCH}_2\text{MgBr}$ )<sup>18</sup> were screened, but none afforded the desired product. Instead, the undesired retro-aldol reaction would occur preferentially to yield **11** in quantitative yield.

To avoid this undesired side reaction, we next turned our attention to the protection of alcohol **12** at an early stage (Scheme 4). First, compound **12** was treated with  $\text{Ac}_2\text{O}$ <sup>19</sup> in the presence of triethylamine (TEA) in DCM afforded **15** in 90% yield. Subsequent treatment of **15** with sodium borohydride ( $\text{NaBH}_4$ )<sup>20</sup> in MeOH gave alcohol **16** in 90% yield (d.r. = 3 : 2). As planned ahead, removal of the hydroxyl group in **16** using Barton–McCombie radical deoxygenation<sup>21</sup> and a subsequent KOH (dissolved in MeOH solution) workup delivered desired product **9** in 50% yield for two steps. Next, the oxidation of primary hydroxyl group in **9** using pyridinium chlorochromate (PCC)<sup>22</sup> in DCM afforded desired aldehyde **17** in 75% yield. With **17** in hand, we continued toward the final stage of the total synthesis of (1*S*,2*S*,4*S*)- $\beta$ -elemene (**3**) *via* Wittig olefination. Gratifyingly, treatment of **17** with  $\text{PPh}_3\text{PCH}_2\text{Br}$  and *n*-BuLi in THF,<sup>18</sup> gave **3** in 82% yield, completing the first and asymmetric total synthesis of **3**. The <sup>1</sup>H and <sup>13</sup>C NMR spectra of synthetic **3** and its optical rotation (synthetic,  $[\alpha]_{\text{D}}^{20} = +24.5^\circ$  (*c* 1.0, EtOH);

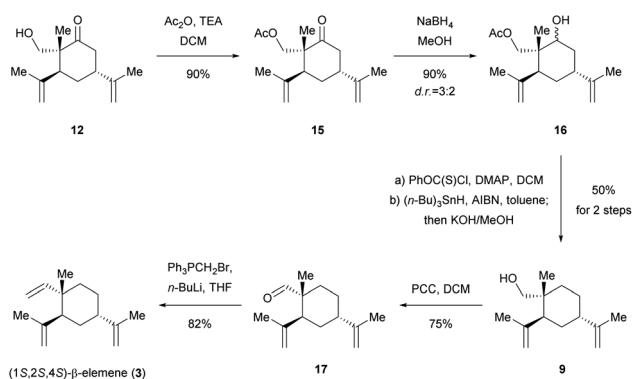


Scheme 1 Asymmetric total syntheses of  $\beta$ -elemene **1–3**.



Scheme 3 Attempts to synthesize advanced intermediate **14**.

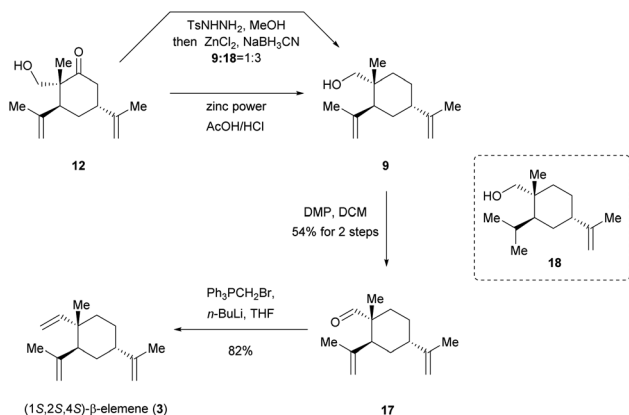


Scheme 4 Eight-step total synthesis of (1*S*,2*S*,4*S*)-β-elemene.

natural,  $[\alpha]_D^{20} = +36.2^\circ$  (*c* 1.4, EtOH)) were in good agreement with those of the isolated natural product.<sup>8</sup> Taken together, an eight-step asymmetric total synthesis of **3** was accomplished in 8.7% overall yield from readily available starting material **8**. Moreover, the structure and absolute configuration of naturally occurring **3** were unambiguously confirmed by our asymmetric total synthesis.

Although (1*S*,2*S*,4*S*)-β-elemene (**3**) has been accomplished in a linear sequence of eight steps from **8**, however, the yield of this protocol was relatively low (8.7% overall yield), and the use of stannyl reagent would put off its acceptability in the pharmaceutical industry. Consequently, we next sought to develop a more practical route to access **3**, which would be more attractive for pharmaceutical manufacturing.

With this target in mind, our new protocol for the total synthesis of (1*S*,2*S*,4*S*)-β-elemene (**3**) is depicted in Scheme 5. In an attempt to the reduction of ketone **12** under standard conditions of Wolff–Kishner–Huang reduction ( $\text{NH}_2\text{NH}_2$ , KOH),<sup>23</sup> decomposition of starting material was observed at the high temperature. Inspired by the elegant work of Kim's group,<sup>24</sup> a zinc-modified cyanoborohydride ( $\text{TsNHNH}_2/\text{ZnCl}_2/\text{NaBH}_3\text{CN}$ ) was developed to be a versatile reducing agent under milder reaction conditions. Pleasingly, the desired product **9** could in fact be achieved, but along with another over-reduced byproduct **18** (**9** : **18** = 1 : 3). We attributed this result to the

Scheme 5 Five-step total synthesis of (1*S*,2*S*,4*S*)-β-elemene.

possible coordination of hydroxyl group and neighbouring double bond with the electrophilic zinc chloride. It was noticed that separation of **9** and **18** by column purification was proved to be difficult. Therefore, we continued to optimize this reaction. Encouraged by Kappe's remarkable work,<sup>25</sup> by using zinc powder (particle size < 45 μm) in acetic acid/hydrochloric acid, ketone **12** was successfully reduced to desired product **9**, which was subsequently subjected to DMP oxidation without further chromatographic purifications, affording aldehyde **17** in 54% yield for two steps. Finally, the Wittig olefination was employed to provide the targeted (1*S*,2*S*,4*S*)-β-elemene (**3**) in 82% yield, completing a five-step asymmetric total synthesis of **3** in 15.5% overall yield. We believed that such a process would be commercially relevant and potentially more practical for pharmaceutical manufacturing.

## Conclusions

In summary, the first total synthesis of (1*S*,2*S*,4*S*)-β-elemene (**3**) was achieved in five steps (15.5% overall yield) or eight steps (8.7% overall yield) from the chiral pool starting material **8**. The stereocenters in **3** were constructed in simple and diastereoselective manners based on the chiral pool strategy. Notably, the transformations involved in our current synthetic routes, including 1,4-Michael conjugate addition, aldol condensation and Wittig olefination are well-developed and viable. Moreover, this work will allow the diverse syntheses of other β-elemene and their analogs to enable further biological research, which is underway and will be reported in due course.

## Experimental section

### General methods

Reagents were purchased at the highest commercial quality (>95%) and used without further purification, unless otherwise stated. Anhydrous tetrahydrofuran (THF), toluene (PhMe) were distilled from sodium-benzophenone, dichloromethane (DCM), methanol (MeOH) were distilled from calcium hydride. All reactions were carried out with magnetic stirring, and if moisture or air sensitive, under an argon atmosphere with dry solvents. External bath temperatures were used to record all reaction temperatures. Low temperature reactions were carried out in a Dewar vessel filled with acetone/dry ice (−78 °C) or distilled water/ice (0 °C). Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Tsingdao silica gel glass-backed plates (60F-254) and visualized under UV light at 254 nm. Staining was performed with an ethanolic solution of phosphomolybdic acid and heat as developing agents. Tsingdao silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Yields refer to chromatographically, unless otherwise specified. NMR spectra were recorded on Bruker Advance 500 (<sup>1</sup>H: 500 MHz, <sup>13</sup>C 125 MHz) and Bruker Advance 400 (<sup>1</sup>H: 400 MHz, <sup>13</sup>C 100 MHz). The spectra were reported as followed: chemical shift δ in ppm (multiplicity, coupling constant *J* in Hz, number of protons) for <sup>1</sup>H NMR spectra and chemical shift δ in ppm for <sup>13</sup>C NMR spectra. The following abbreviations were used to explain the



multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, or combinations thereof. Residual solvent peaks of CDCl<sub>3</sub> ( $\delta$  H = 7.26 ppm,  $\delta$  C = 77.16 ppm) were used as an internal reference, unless otherwise stated. High resolution mass spectrometric (HRMS) data were recorded on a Brüker Apex IV RTMS instrument and a VG Auto Spec-3000 spectrometer, respectively. Optical rotation values were measured with a Jasco P-1020 polarimeter. The specific rotation was calculated as followed:  $[\alpha]_D^{20} = (\alpha \times 100)/(c \times d)$ .

**Synthesis of compound 11.** Isopropenyl Grignard reagent **10** (1.0 M in THF, 133.0 mL, 133.0 mmol, 2.0 equiv.) was added dropwise to a suspension of copper(i) iodide (12.6 g, 66.2 mmol, 1.1 equiv.) in dry THF (300.0 mL) at  $-78$  °C and the resulting mixture was stirred for 1 h at the same temperature. A solution of (*R*)-carvone **8** (10 g, 66.67 mmol, 1.0 equiv.) in dry THF (50.0 mL) was added to the above solution at  $-78$  °C. The reaction was allowed to warm to room temperature and stirred for 3 h, and then quenched with a saturated solution of NH<sub>4</sub>Cl (100 mL). The resultant aqueous layer was extracted with ethyl acetate (3  $\times$  150 mL), and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. The extracts were filtered off and then evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes = 1 : 20  $\rightarrow$  1 : 15) to give compound **11** (8.9 g) as a pale yellow oil in 70% yield.  $R_f$  = 0.45 (silica gel, EtOAc/hexanes = 1 : 6);  $[\alpha]_D^{20} = -4.5^\circ$  (c 0.50, CDCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  4.93 (s, 1H), 4.80 (s, 1H), 4.73 (s, 1H), 4.52 (s, 1H), 2.71 (d,  $J$  = 5.1 Hz, 1H), 2.65 (d,  $J$  = 4.6 Hz, 1H), 2.62–2.57 (m, 1H), 2.53 (m, 1H), 2.34–2.27 (m, 1H), 2.03–1.96 (m, 1H), 1.86–1.79 (m, 1H), 1.73 (s, 3H), 1.70 (s, 3H), 1.07 (d,  $J$  = 6.9 Hz, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  213.7, 147.5, 144.1, 112.9, 110.6, 47.2, 46.6, 45.1, 40.5, 32.1, 23.9, 21.3, 12.1; IR  $\nu_{\max}$  (film) 3082, 2986, 2935, 1706, 1646, 1377, 901 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>13</sub>H<sub>21</sub>O [M + H]<sup>+</sup>: 193.1587; found: 193.1589.

**Synthesis of compound 12.** KOH (4.6 g, 82.1 mmol, 2.0 equiv.) was dissolved in MeOH (200 mL) and a solution of **11** in MeOH (10.0 mL) was slowly added at 0 °C. The resulting mixture was stirred for 30 min and a solution of formalin (39% in H<sub>2</sub>O, 9.4 mL, 125.1 mmol, 3.0 equiv.) was added in a dropwise manner. The reaction mixture was stirred for 1.5 h at the same temperature and then quenched with a saturated solution of NH<sub>4</sub>Cl (30.0 mL). After removal of methanol under vacuum, the mixture was then extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  50.0 mL), and the combined extracts were dried over Na<sub>2</sub>SO<sub>4</sub>. The extracts were filtered off and then evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes = 1 : 20  $\rightarrow$  1 : 10) to give compound **12** (4.6 g) as a pale yellow oil in 50% cumulative yield (the recovery of starting material **11** was ran for three cycles).  $R_f$  = 0.35 (silica gel, EtOAc/hexanes = 1 : 6);  $[\alpha]_D^{20} = +3.5^\circ$  (c 0.45, CDCl<sub>3</sub>); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.95 (s, 1H), 4.87 (s, 1H), 4.74 (s, 1H), 4.70 (s, 1H), 3.67 (d,  $J$  = 11.5 Hz, 1H), 3.43 (d,  $J$  = 11.5 Hz, 1H), 2.75–2.69 (m, 1H), 2.69–2.63 (m, 2H), 2.60–2.51 (m, 1H), 2.45 (s, 1H), 2.14 (m, 1H), 1.84 (d,  $J$  = 14.3 Hz, 1H), 1.76 (s, 3H), 1.71 (s, 3H), 1.05 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  217.2, 146.4, 144.4, 114.8, 112.5, 66.5, 53.7, 42.7, 42.1, 40.4, 28.8, 24.0, 22.1, 16.7; IR  $\nu_{\max}$  (film)

3445, 2975, 2875, 2364, 1714, 1456, 999 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>14</sub>H<sub>23</sub>O<sub>2</sub>Na [M + Na]<sup>+</sup>: 245.1512; found: 245.1512.

**Synthesis of compound 13.** To a solution of **12** (500 mg, 2.25 mmol, 1.0 equiv.) in dry DCM (20.0 mL) was added DMP (1.15 g, 2.7 mmol, 1.2 equiv.) at 0 °C. The reaction was allowed to warm to room temperature and stirred for 1 h, then quenched with sat. aq. Na<sub>2</sub>SO<sub>3</sub> (10.0 mL). The resultant aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  20.0 mL), and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. The extracts were filtered off and then evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes = 1 : 40  $\rightarrow$  1 : 20) to give compound **13** (346 mg) as a colorless oil in 70% yield.  $R_f$  = 0.55 (silica gel, EtOAc/hexanes = 1 : 6);  $[\alpha]_D^{20} = +2.5^\circ$  (c 0.50, CDCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  9.39 (d,  $J$  = 1.1 Hz, 1H), 4.97 (s, 1H), 4.80 (s, 1H), 4.70 (s, 1H), 4.51 (s, 1H), 2.99 (t,  $J$  = 5.0 Hz, 1H), 2.76–2.67 (m, 1H), 2.55 (dd,  $J$  = 14.9, 4.9 Hz, 1H), 2.49–2.40 (m, 1H), 1.92 (dt,  $J$  = 13.9, 4.7 Hz, 1H), 1.86–1.77 (m, 1H), 1.70 (s, 3H), 1.69 (s, 3H), 1.19 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  209.8, 199.8, 146.6, 142.4, 114.8, 111.3, 64.0, 45.8, 44.5, 40.0, 30.1, 24.4, 21.0, 14.4; IR  $\nu_{\max}$  (film) 2931, 1745, 1715, 1373, 1178, 990 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>14</sub>H<sub>21</sub>O<sub>2</sub> [M + H]<sup>+</sup>: 221.1536; found: 221.1538.

**Synthesis of compound 15.** To a stirred solution of **12** (4.6 g, 20.7 mmol, 1.0 equiv.) and TEA (8.6 mL, 62.2 mmol, 3.0 equiv.) in DCM (100 mL) was added acetic anhydride (4.0 mL, 41.4 mmol, 2.0 equiv.) at 0 °C. The resulting mixture was allowed to warm to room temperature and stirred overnight. Then the resultant reaction mixture was diluted by sat. aq. NaHCO<sub>3</sub> (50.0 mL) and subsequently extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  50.0 mL). The combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified using flash column chromatography on silica gel (EtOAc/hexanes = 1 : 50  $\rightarrow$  1 : 30) to give compounds **15** (4.9 g) as a colorless oil in 90% yield.  $R_f$  = 0.75 (silica gel, EtOAc/hexanes = 1 : 6);  $[\alpha]_D^{20} = +1.5^\circ$  (c 0.65, CDCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  4.92–4.88 (m, 1H), 4.80 (s, 1H), 4.64 (s, 1H), 4.57 (s, 1H), 4.21 (d,  $J$  = 10.9 Hz, 1H), 3.96 (d,  $J$  = 10.9 Hz, 1H), 2.73–2.63 (m, 2H), 2.52 (t,  $J$  = 5.6 Hz, 2H), 2.02–1.95 (m, 1H), 1.94 (s, 3H), 1.85 (m, 1H), 1.68 (s, 6H), 1.01 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>)  $\delta$  212.5, 170.6, 146.6, 144.0, 114.8, 111.5, 67.1, 51.2, 44.2, 42.4, 40.1, 28.9, 23.9, 21.6, 20.7, 17.2; IR  $\nu_{\max}$  (film) 2925, 2854, 1768, 1377, 1024, 999 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>16</sub>H<sub>24</sub>O<sub>3</sub>Na [M + Na]<sup>+</sup>: 287.1618; found: 287.1615.

**Synthesis of compound 16.** To a stirred solution of **15** (3.0 g, 11.3 mmol, 1.0 equiv.) in MeOH/THF (80.0/20.0 mL) was added NaBH<sub>4</sub> (0.86 g, 22.6 mmol, 2.0 equiv.) at  $-10$  °C. The mixture was stirred for 15 min at  $-10$  °C and 30 min at room temperature, after which time it was quenched with the saturated NH<sub>4</sub>Cl solution (20.0 mL). The resultant aqueous layer was extracted with ethyl acetate (3  $\times$  50.0 mL), and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. The extracts were filtered off and then evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes = 1 : 20  $\rightarrow$  1 : 15) to give mixture of diastereomers **16** (2.7 g, d.r. = 3 : 2) as a pale yellow oil in 90% yield.  $R_f$  = 0.40 (silica gel, EtOAc/hexanes = 1 : 6); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  4.90 (s, 2H), 4.87 (s, 0.8H), 4.85–4.79 (m, 2.5H), 4.73 (d,  $J$  = 9.9 Hz, 2H),



4.36 (d,  $J = 11.4$  Hz, 1H), 4.20 (d,  $J = 10.9$  Hz, 0.7H), 4.00 (d,  $J = 10.9$  Hz, 0.7H), 3.76 (dd,  $J = 6.5, 3.9$  Hz, 0.7H), 3.55 (dd,  $J = 12.0, 3.8$  Hz, 2H), 2.71 (s, 1H), 2.61–2.53 (m, 0.7H), 2.43 (s, 1H), 2.41–2.37 (m, 0.7H), 2.30 (dd,  $J = 13.4, 3.0$  Hz, 1H), 2.06 (s, 3H), 2.04 (s, 2.3H), 2.03–1.98 (m, 1H), 1.96–1.81 (m, 3H), 1.80 (s, 2H), 1.77 (s, 2H), 1.73 (s, 3H), 1.71–1.67 (m, 1H), 1.03 (s, 2H), 0.84 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  172.2, 171.5, 149.45, 146.47, 146.45, 145.48, 114.1, 114.0, 110.7, 109.5, 73.4, 69.0, 67.4, 67.3, 43.5, 42.5, 41.9, 41.3, 38.3, 38.1, 31.6, 30.96, 29.7, 28.6, 24.6, 23.2, 22.8, 22.1, 21.1, 21.0, 18.2, 9.8; IR  $\nu_{\text{max}}$  (film) 3435, 2930, 2856, 1427, 1083, 859  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{16}\text{H}_{26}\text{O}_3\text{Na}$   $[\text{M} + \text{Na}]^+$ : 289.1774; found: 289.1772.

**Synthesis of compound 9.** To a solution of compound **16** (1.5 g, 5.64 mmol, 1.0 equiv.) in DCM (30.0 mL) was added DMAP (1.37 g, 11.28 mmol, 2.0 equiv.), phenyl chlorothionocarbonate (1.94 g, 11.28 mmol, 2.0 equiv.) at room temperature. The resulting mixture was stirred overnight and filtered through a pad of silica gel (eluent: EtOAc). The organic solvent was removed under reduced pressure and the resultant residue was dissolved in toluene (20.0 mL). Then the reaction mixture was heated to reflux and tributyltin hydride (3.30 g, 11.28 mmol, 2.0 equiv.) and AIBN (370 mg, 11.28 mmol, 0.2 equiv.) was added. After being stirring for 8 h, a solution of KOH (1.0 g) in MeOH (20.0 mL) was added and stirred for 2 h. The reaction mixture was diluted by water (20.0 mL) and the aqueous layer was extracted with ethyl acetate (3  $\times$  30.0 mL), and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ . The extracts were filtered off and then evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes = 1 : 50  $\rightarrow$  1 : 20) to give compound **9** (500 mg) as a white solid in 50% yield for two steps.  $R_f = 0.30$  (silica gel, EtOAc/hexanes = 1 : 10);  $[\alpha]_{\text{D}}^{20} = +7.5^\circ$  (c 0.60,  $\text{CDCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.88 (d,  $J = 1.3$  Hz, 1H), 4.82 (s, 1H), 4.79 (s, 1H), 4.76 (d,  $J = 1.5$  Hz, 1H), 3.39–3.30 (m, 2H), 2.35 (s, 1H), 2.28 (dd,  $J = 10.9, 3.7$  Hz, 1H), 1.81 (m, 2H), 1.76 (s, 3H), 1.72 (s, 3H), 1.71–1.62 (m, 3H), 1.56–1.48 (m, 1H), 1.17 (dd,  $J = 9.1, 4.1$  Hz, 1H), 0.94 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  149.2, 147.2, 112.9, 110.5, 72.3, 44.8, 39.0, 38.9, 31.8, 29.9, 23.9, 23.3, 22.5, 17.9; IR  $\nu_{\text{max}}$  (film) 2995, 1755, 1249, 1240, 764, 748  $\text{cm}^{-1}$ ; IR  $\nu_{\text{max}}$  (film) 3427, 2933, 2857, 1427, 1063, 990  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{14}\text{H}_{25}\text{O}$   $[\text{M} + \text{H}]^+$ : 209.1900; found: 209.1900.

**Synthesis of compound 17 (method A).** To a solution of **9** (410 mg, 1.97 mmol, 1.0 equiv.) in dry DCM (20.0 mL) was added PCC (847 mg, 3.94 mmol, 2.0 equiv.) and silica gel (200–300 mesh, 200 mg) at 0  $^\circ\text{C}$ . The reaction mixture was allowed to warm to room temperature and stirred for 3 h, and then filtered through a pad of silica gel (eluent:  $\text{CH}_2\text{Cl}_2$ ). The organic solvent was removed under reduced pressure and purified by flash chromatography on silica gel (EtOAc/hexanes = 1 : 80  $\rightarrow$  1 : 50) to give compound **17** (314 mg) as a white solid in 75% yield.  $R_f = 0.60$  (silica gel, EtOAc/hexanes = 1 : 10);  $[\alpha]_{\text{D}}^{20} = +8.5^\circ$  (c 0.25,  $\text{CDCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.39 (s, 1H), 4.91–4.88 (m, 1H), 4.82 (d,  $J = 1.2$  Hz, 1H), 4.77 (s, 1H), 4.74 (s, 1H), 2.67 (dd,  $J = 7.2, 4.8$  Hz, 1H), 2.38–2.28 (m, 1H), 1.93–1.84 (m, 1H), 1.74 (s, 3H), 1.70 (s, 3H), 1.68–1.70 (m, 4H), 1.39 (m, 1H), 1.00 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  206.4, 147.9, 146.3, 113.6, 110.1, 49.5, 42.5, 38.5, 30.5, 29.4, 25.4, 24.9, 21.8, 17.1; IR  $\nu_{\text{max}}$  (film)

2915, 1735, 1680, 1435, 1202, 980  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{14}\text{H}_{23}\text{O}$   $[\text{M} + \text{H}]^+$ : 207.1743; found: 207.1742.

**Synthesis of compound 17 (method B).** To a solution of **12** (400 mg, 1.8 mmol, 1.0 equiv.) in ethanol (20.0 mL), glacial acetic acid (10.0 mL) and conc. hydrochloric acid (1.0 mL). The mixture was heated to 80  $^\circ\text{C}$  and under stirring zinc powder (2.0 g, particle size < 45  $\mu\text{m}$ ) was added in small portion (each about 0.1 g). The overall time of the zinc addition is about 2 h. When the addition was finished, the reaction mixture was heated under reflux for 10 min and filtered still hot from excess of zinc. The filtrate was concentrated and the resultant residue was dissolved in DCM (20.0 mL), then DMP (916 mg, 2.16 mmol, 1.2 equiv.) was added at 0  $^\circ\text{C}$ . The reaction mixture was allowed to warm to room temperature and stirred for 1 h, then quenched with sat. aq.  $\text{Na}_2\text{SO}_3$  (10.0 mL). The resultant aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (3  $\times$  20.0 mL), and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ . The extracts were filtered off and then evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes = 1 : 80  $\rightarrow$  1 : 50) to give compound **17** (200 mg) as a white solid in 54% yield for two steps.

**Synthesis of compound 18.** To a solution of **12** (500 mg, 2.25 mmol, 1.0 equiv.) and (*p*-tolylsulfonyl)hydrazine (462 mg, 2.48 mmol, 1.1 equiv.) in MeOH (20.0 mL) at room temperature was slowly added a suspended solution of zinc chloride (153 mg, 1.12 mmol, 0.5 equiv.) and sodium cyanoborohydride (159 mg, 2.48 mmol, 1.1 equiv.) in MeOH (10.0 mL). After being stirred for 10 min, the solution was heated to reflux for 1 h and then treated with 0.1 N NaOH (20.0 mL). The resultant aqueous layer was extracted with ethyl acetate (3  $\times$  20.0 mL), and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ . The extracts were filtered off and then evaporated under vacuum. The residue was purified by flash chromatography on silica gel (EtOAc/hexanes = 1 : 50  $\rightarrow$  1 : 30) to give a mixture of **9** and **18** (200 mg) as a pale yellow oil, the  $^1\text{H}$  NMR spectrum indicated their ratio is 1 : 3 (**9** : **18**),  $R_f = 0.50$  (silica gel, EtOAc/hexanes = 1 : 8).

Compound **18** was isolated for characterization purpose by taking an aliquot from the combined organic layers, followed by concentration under reduced pressure and the residue was purified by PTLC (silica gel, EtOAc/hexanes = 1 : 10) to give **18** as a colorless oil.  $R_f = 0.60$  (silica gel, EtOAc/hexanes = 1 : 8);  $[\alpha]_{\text{D}}^{20} = +3.5^\circ$  (c 0.35,  $\text{CDCl}_3$ );  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.87–4.78 (m, 1H), 4.78–4.70 (m, 1H), 3.35 (s, 2H), 2.27 (dd,  $J = 11.6, 3.6$  Hz, 1H), 1.74 (s, 3H), 1.73–1.61 (m, 2H), 1.61–1.46 (m, 5H), 1.31–1.25 (m, 1H), 1.09 (d,  $J = 12.3$  Hz, 1H), 0.92 (s, 3H), 0.87 (t,  $J = 6.9$  Hz, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  149.4, 112.8, 72.4, 44.1, 40.4, 38.8, 31.4, 29.7, 26.8, 23.6, 23.2, 21.4, 21.2, 17.8; IR  $\nu_{\text{max}}$  (film) 2925, 2855, 1732, 1250, 1024, 986  $\text{cm}^{-1}$ ; HRMS (ESI) calcd for  $\text{C}_{14}\text{H}_{26}\text{NaO}$   $[\text{M} + \text{Na}]^+$ : 233.1876; found: 233.1876.

**Synthesis of compound (1S,2S,4S)- $\beta$ -elemene (3).** To a solution of methyltriphenylphosphonium bromide (571 mg, 1.60 mmol, 2.2 equiv.) in THF (10.0 mL) was added *n*-BuLi (50.0 mL of 2.5 M in hexanes, 125 mmol, 1.25 equiv.) dropwise over 5 min at  $-78$   $^\circ\text{C}$ . After 30 min stirring at this temperature, the reaction was allowed to warm to room temperature and keep stirring for another 20 min. Then the reaction was cooled to



–78 °C again and a solution of **17** (9.40 mL, 150 mmol, 1.50 equiv.) in dry THF (2.0 mL) was added. The mixture was allowed warm to room temperature again over 1 h and quenched with sat. aq. NH<sub>4</sub>Cl (5.0 mL). The resultant aqueous layer was extracted with ethyl acetate (3 × 15.0 mL), and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub>. The extracts were filtered off and then evaporated under vacuum. The residue was purified by flash chromatography on silica gel (100% hexanes) to give (1*S*,2*S*,4*S*)-β-elemene (121 mg) as a colorless liquid in 82% yield. *R*<sub>f</sub> = 0.95 (silica gel, 100% hexanes); [α]<sub>D</sub><sup>20</sup> = +24.5° (c 1.0, EtOH); <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.82 (dd, *J* = 17.5, 11.0 Hz, 1H), 4.93 (dd, *J* = 8.3, 1.0 Hz, 1H), 4.90 (s, 1H), 4.86 (d, *J* = 1.2 Hz, 1H), 4.84 (m, 1H), 4.79 (s, 1H), 4.68 (s, 1H), 2.40–2.32 (m, 1H), 2.18 (m, 1H), 1.75 (s, 3H), 1.73 (s, 3H), 1.57–1.78 (m, 5H), 1.32 (m, 1H), 1.02 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 150.2, 148.2, 147.9, 112.4, 110.17, 110.15, 47.7, 39.8, 39.1, 34.7, 30.2, 25.5, 24.6, 22.30, 22.29; IR ν<sub>max</sub> (film) 3082, 2965, 1644, 1442, 1374, 909 cm<sup>-1</sup>; HRMS (ESI) calcd for C<sub>15</sub>H<sub>25</sub> [M + H]<sup>+</sup>: 205.1951; found: 205.1952. The spectra of <sup>1</sup>H NMR and <sup>13</sup>C NMR of synthetic **3** are well in accord with the isolated natural product.<sup>8</sup>

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

This work was supported by the China Postdoctoral Science Foundation (No. 2020M682925). We would also like to thank Dr C. G. Jiang at XtalPi for his kindly help and useful discussions.

## Notes and references

- (a) W. Tan, J. J. Lu, M. Q. Huang, Y. B. Li, M. W. Chen, G. S. Wu, J. Gong, Z. F. Zhong, Z. T. Xu, Y. Y. Dang, J. J. Guo, X. P. Chen and Y. T. Wang, *Chin. Med.*, 2011, **6**, 27; (b) C.-Y. Shen, J.-G. Jiang, L. Yang, D.-W. Wang and W. Zhu, *Br. J. Pharmacol.*, 2017, **174**, 1395–1425; (c) C.-L. Yao, J.-Q. Zhang, J.-Y. Li, W.-L. Wei, S.-F. Wu and D.-A. Guo, *Nat. Prod. Rep.*, 2021, **38**, 1618–1633.
- For selected reviews on elemenes, see: (a) J.-J. Lu, Y.-Y. Dang, M. Huang, W.-S. Xu, X.-P. Chen and Y.-T. Wang, *J. Ethnopharmacol.*, 2012, **143**, 406–411; (b) Z. Y. Jiang, J. A. Jacob, D. S. Loganathachetti, P. Nainangu and B. A. Chen, *Front. Pharmacol.*, 2017, **8**, 105; (c) B. T. Zhai, Y. Y. Zeng, Z. W. Zeng, N. N. Zhang, C. X. Li, Y. J. Zeng, Y. You, S. L. Wang, X. B. Chen, X. B. Sui and T. Xie, *Int. J. Nanomed.*, 2018, **13**, 6279–6296; (d) B. T. Zhai, N. N. Zhang, X. M. Han, Q. J. Li, M. M. Zhang, X. Y. Chen, G. H. Li, R. N. Zhang, P. Chen, W. G. Wang, C. X. Li, Y. Xiang, S. P. Liu, T. Duan, J. S. Lou, T. Xie and X. B. Sui, *Biomed. Pharmacother.*, 2019, **114**, 108812; (e) Z. Q. Bai, C. S. Yao, J. L. Zhu, Y. Y. Xie, X.-Y. Ye, R. R. Bai and T. Xie, *Molecules*, 2021, **26**, 1499.
- (a) M. Adio, *Tetrahedron*, 2009, **65**, 5145–5159; (b) W. Chen, J.-B. Wang, Z. Feng and Q. Liu, *Chin. J. Syn. Chem.*, 2021, **29**, 802–812.
- (a) L. Huang, *US Pat.*, US8507562B2, 2013; (b) H. Cai, L. L. Ren, Y. Wang and Y. J. Zhang, *Front. Oncol.*, 2021, **11**, 571476.
- (a) X. M. Yu, M. Y. Xu, N. Li, Z. J. Li, H. Y. Li, S. J. Shao, K. Zou and L. J. Zou, *Biochem. Biophys. Res. Commun.*, 2017, **490**, 514–520; (b) Y. Zhou, T. Takano, Y. Wang, X. Li, R. Wang, Y. Wakatsuki, H. Nakajima-Adachi, M. Tanokura, T. Miyakawa and S. Hachimura, *iScience*, 2021, **24**, 101883; (c) Y. Y. Zhou, W. Y. Qiu, Y. M. Wang, R. Wang, T. Takano, X. Y. Li, Z. L. Zhu, H. Nakajima-Adachi, M. Tanokura, S. Hachimura and T. Miyakawa, *Biomedicines*, 2021, **9**, 704.
- (a) B. Wang, J. Guo, J. Di and Q. Shi, *Chin. Clin. Cancer*, 1999, **26**, 10–13; (b) T.-Z. Zhu, X.-M. Li, L. H. Luo, Y.-H. Xu, P. Cao, Y. Liu and G.-B. Liang, *Mol. Med. Rep.*, 2014, **10**, 1122–1128; (c) G. N. Zhang, C. R. A. Jr, Y. K. Zhang, Z. S. Chen and H. Guo, *Chin. J. Cancer*, 2015, **34**, 488–495.
- A. J. Weinheimer, W. W. Youngblood, P. H. Washecheck, T. K. B. Karns and L. S. Ciereszko, *Tetrahedron Lett.*, 1970, **11**, 497–500.
- Y. M. Shi, R. Y. Wang, X. Feng, X. T. Chen, J. Li, A. L. He, J. Shi, Y. M. Yuan, Y. C. Wang and S. Liu, *CN Pat.*, CN109438166B, 2021.
- For selected total syntheses of (±)-β-elemene, see: (a) O. P. Vig, B. Ram, K. S. Atwal and S. S. Bari, *J. Indian Chem. Soc.*, 1975, **52**, 257–260; (b) J. E. McMurry and P. Kočovský, *Tetrahedron Lett.*, 1985, **26**, 2171–2172; (c) D. Kim, J. Lee, J. Chang and S. Kim, *Tetrahedron*, 2001, **57**, 1247–1252; (d) A. F. Barrero, M. M. Herrador, J. F. Quilez del Moral, P. Arteaga, N. Meine, M. C. Perez-Morales and J. V. Catalán, *Org. Biomol. Chem.*, 2011, **9**, 1118–1125; (e) D. P. Iglesias, P. H. Teijón, R. R. González and A. Fernández-Mateos, *Eur. J. Org. Chem.*, 2018, **35**, 4926–4932.
- K. S. Kulkarni and A. S. Rao, *Tetrahedron*, 1965, **21**, 1167–1173.
- E. J. Corey, B. E. Roberts and B. R. Dixon, *J. Am. Chem. Soc.*, 1995, **117**, 193–196.
- L. Q. Huang, X. Ke, Q. S. Gao, X. Wang, X. Y. Song, D. J. Wang, J. Yang, J. Guo, Y. N. Wang and Z. F. Shi, *CN Pat.*, CN111423300A, 2020.
- For selected books and reviews on chiral pool synthesis, see: (a) S. Hanessian, *Total Synthesis of Natural Products: The 'Chiron' Approach*, ed. J. E. Baldwin, Pergamon, Oxford, UK, 1983; (b) Z. G. Brill, M. L. Condakes, C. P. Ting and T. J. Maimone, *Chem. Rev.*, 2017, **117**, 11753–11795; (c) C. N. Stout and H. Renata, *Acc. Chem. Res.*, 2021, **54**(5), 1143–1156; (d) A. Gogoi, S. Mezhubeinuo, S. Nongrum and G. Bez, *Curr. Org. Chem.*, 2021, **25**, 1566–1610.
- (a) H.-J. Knölker, A. Ecker, P. Struwe, A. Steinmeyer, G. Müller and G. Neef, *Tetrahedron*, 1997, **53**, 91–108; (b) H. Shi, C. H. Tan, W. B. Zhang, Z. C. Zhang, R. Long, J. X. Gong, T. P. Luo and Z. Yang, *J. Org. Chem.*, 2016, **81**, 751–771.
- N. Krause, *Angew. Chem., Int. Ed.*, 1994, **33**, 1764–1765.
- L. Kürti, B. Czako and E. J. Corey, *Org. Lett.*, 2008, **10**, 5247–5250.
- Z. Y. Zhou, A. X. Gao and S. A. Snyder, *J. Am. Chem. Soc.*, 2019, **141**, 7715–7720.



## Paper

- 18 K. C. Nicolaou, S. Y. Pan, Y. Shelke, Q. J. Ye, D. Das and S. Rigol, *J. Am. Chem. Soc.*, 2021, **143**, 20970–20979.
- 19 C. C. Yuan, S. Y. Zhong, X. Y. Li, Y. H. Wang, M.-M. Xun, Y. L. Bai and K. K. Zhu, *Org. Biomol. Chem.*, 2018, **16**, 7843–7850.
- 20 J. Y. Liu, J. L. Wu, J.-H. Fan, X. Yan, G. J. Mei and C.-C. Li, *J. Am. Chem. Soc.*, 2018, **140**, 5365–5369.
- 21 T. R. R. Pettus, M. Inoue, X.-T. Chen and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2000, **122**, 6160–6168.
- 22 M. E. Fox, C. Li, J. P. Marino and L. E. Overman, *J. Am. Chem. Soc.*, 1999, **121**, 5467–5480.
- 23 M. Toyota, T. Wada and M. Ihara, *J. Org. Chem.*, 2000, **65**, 4565–4570.
- 24 S. Kim, H. C. Oh, J. S. Ko, K. H. Ahn and Y. J. Kim, *J. Org. Chem.*, 1985, **50**, 1927–1932.
- 25 T. Kappe, R. Aigner, P. Roschger, B. Schnell and W. Stadibauer, *Tetrahedron*, 1995, **51**, 12923–12928.

