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ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/gnpl20

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To cite this article: Xiaofeng Guo, Zhiwei Xue, Dongdong Xu, Qidong Tu, Honghong Chang, Xihua Yang & Shuangping Huang (2021): Total synthesis of (–)-brazilane via a lipase-catalyzed desymmetrisation reaction, Natural Product Research, DOI: 10.1080/14786419.2021.1922403

To link to this article: https://doi.org/10.1080/14786419.2021.1922403

NATURAL PRODUCT RESEARCH
https://doi.org/10.1080/14786419.2021.1922403

Total synthesis of (–)-brazilane via a lipase-catalyzed desymmetrisation reaction

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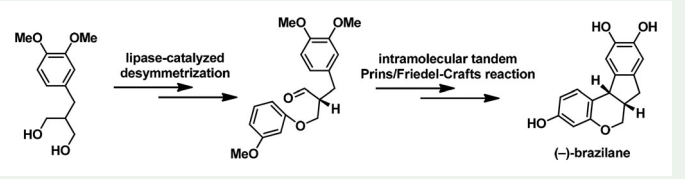
ABSTRACT

Herein, we described the asymmetric total synthesis of (–)-brazilane, an optically active natural product. The key steps of this synthetic approach are a lipase-catalyzed desymmetrisation reaction of a prochiral diol using vinyl acetate to prepare a chiral primary alcohol and a trifluoroacetic acid-catalyzed one pot intramolecular tandem Prins/Friedel-Crafts reaction used to construct the *cis*-fused chromane and indane framework.



ARTICLE HISTORY
Received 17 December 2020
Accepted 22 April 2021

KEYWORDS
Total synthesis; (–)-brazilane; natural product; lipase-catalyzed desymmetrisation; tandem Prins/Friedel-Crafts reaction

1. Introduction

Natural products containing a homoisoflavonoid skeleton possess novel biological activities and play an important role in pharmaceutical research and applications (Abegaz et al. 2007). As important members of the homoisoflavonoid family of natural products, tetracyclic brazilane and its related compounds (Figure 1) have demonstrated a series of outstanding bioactivities. For example, brazilin shows anti-inflammatory (Bae et al. 2005), hypoglycemic (Moon et al. 1993; Kim et al. 1998), vasorelaxant (Hu et al. 2003), antibacterial (Xu and Lee 2004), antitumor (Kim et al. 2012; Lee et al. 2013) and neuroprotection activities (Liu et al. 2019; Henríquez et al. 2020). Brazilane and its related compounds (Figure 1) are found in the alcoholic extracts of heartwood of *Caesalpinia sappan* L. (Legminosae), which is also a famous traditional Chinese medicine used for treatment of emmeniopathy, convulsions, straumatic disease and menstrual disorders.

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Supplemental data for this article can be accessed online at https://doi.org/10.1080/14786419.2021.1922403.

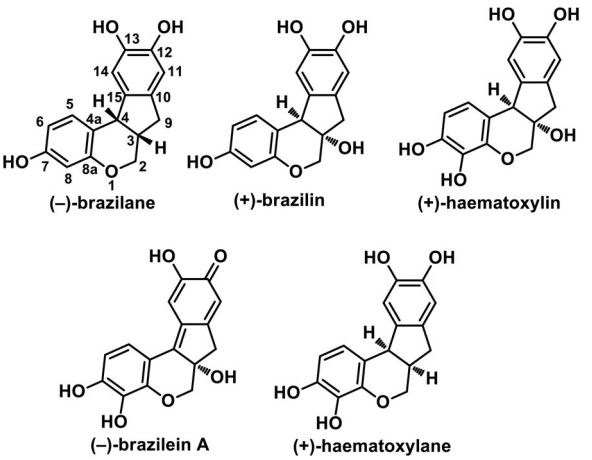
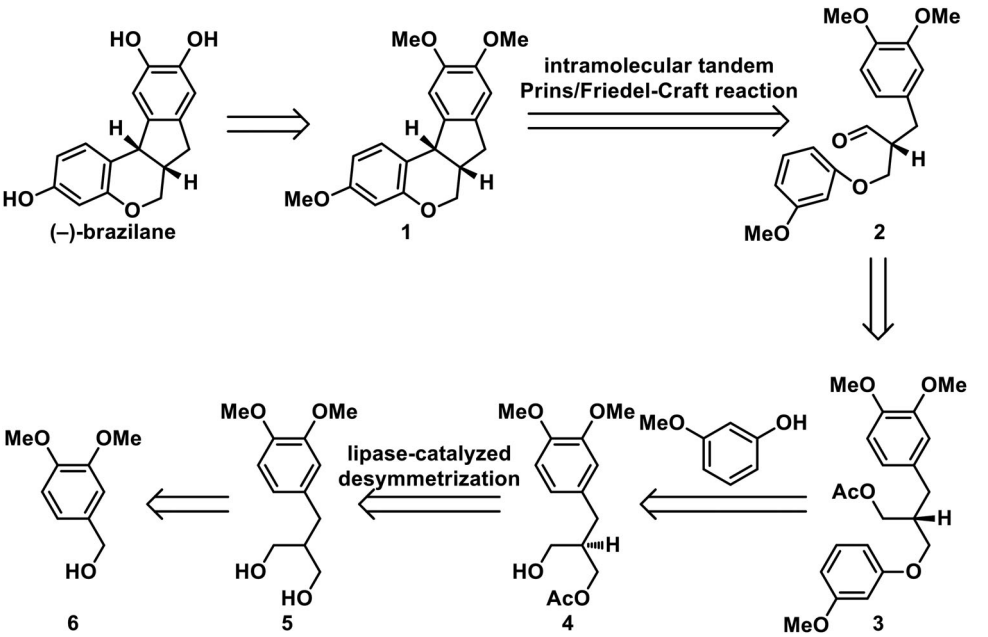


Figure 1. Structures of brazilane and some selected homoisoflavonoids.

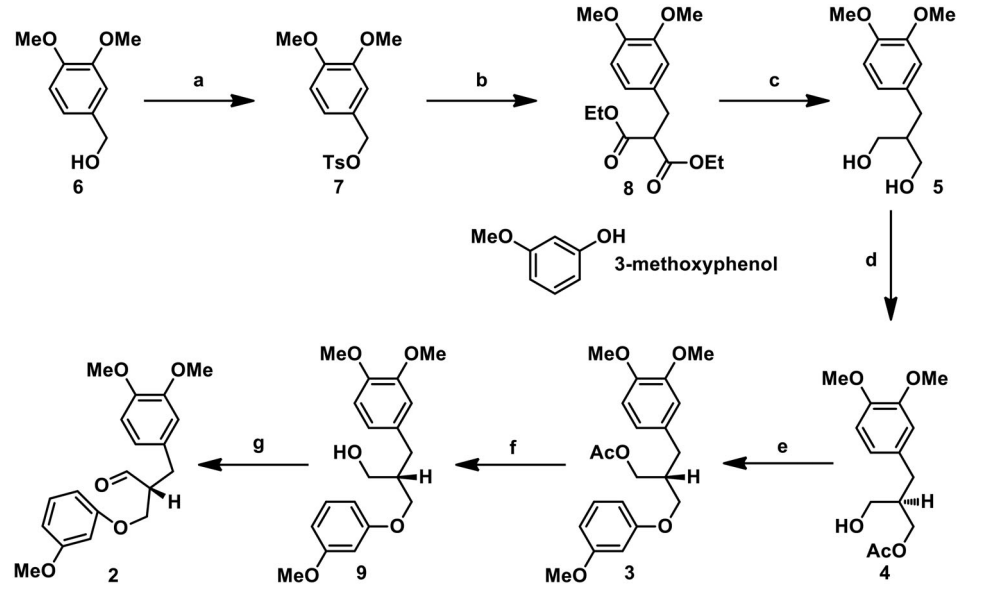
Structurally, brazilane is the reduced counterpart of this family of compounds bearing an H-atom instead of a hydroxyl group at the C-3 position. Our research interest has focused on studying the structure-activity relationships of natural products and their potential pharmaceutical properties through total synthesis. We have recently accomplished a novel synthetic approach to (+)-brazilin employing a Sharpless asymmetric dihydroxylation to introduce the chiral center and a one pot trifluoroacetic acid-catalyzed intramolecular tandem Prins/Friedel-Craft reaction as the key steps (Huang et al. 2020). Considering that brazilane possesses the basic skeleton of its family of natural products, the development of a practicable synthetic route to brazilane may inspire the synthesis of other related family members or functionalised derivatives. To the best of our knowledge, only three racemic total syntheses of brazilane (Lin et al. 2008; Yadav et al. 2014; Kim and Kim 2018) and two semi-syntheses (Morsingh and Robinson 1970; Xu and Yadan 1996) have been published to date with no asymmetric total synthesis previously reported. Herein, we describe an efficient and practicable asymmetric synthetic route to (–)-brazilane using a non-toxic enzymatic reaction as the key step.

Our retrosynthesis of brazilane is depicted in Scheme 1. We envisioned that (–)-brazilane may arise from its O-methyl ether (**1**) via its deprotection (Kim and Kim 2018). The *cis*-fused chromane and indane framework of **1** can be accessed via an intramolecular tandem Prins/Friedel-Craft reaction from aldehyde **2** (Huang et al. 2020), which can be obtained from intermediate **3** following a simple sequence of reactions. Intermediate **3** was disconnected into 3-methoxyphenol and alcohol **4**, while the acetyl group in **4** can be assumed to be installed using a lipase-catalyzed desymmetrisation reaction of diol **5** (Kawasaki et al. 2013), which can be easily synthesised from 3,4-dimethoxybenzyl alcohol (**6**).

Scheme 2 shows the synthesis was started from commercially available 3,4-dimethoxybenzyl alcohol (**6**). The hydroxyl group in **6** was converted into its corresponding tosylate (**7**) upon reaction with tosyl chloride in the presence of triethylamine in CH_2Cl_2 in 83% yield (Rosowsky et al. 1998). Diethyl malonate undergoes an S_N2 reaction with **7** using sodium hydride as base in a mixed solvent comprised of THF-DMF (1:1) to give diethyl ester **8**, in which the double ethyl ester groups were both reduced using lithium aluminum hydride in dry THF at room temperature to afford diol **5** in



Scheme 1. Retrosynthetic analysis of (–)-brazilane.



Scheme 2. *Reagents and conditions*: (a) TsCl, Et_3N, DMAP, DCM, r.t., 83%; (b) NaH, diethyl malonate, THF-DMF (1:1), 0 °C to r.t., 90%; (c) $LiAlH_4$, THF, 0 °C to r.t., 87%; (d) Lipase PS, vinyl acetate, r.t., 99%, 96% ee; (e) 1,1′-(Azodicarbonyl)-dipiperidine, Bu_3P, THF, 70 °C, 87%; (f) K_2CO_3, MeOH, r.t., 89%; (g) DMP, CH_2Cl_2, r.t, 83%.

87% yield (Itoh et al. 1993). Retrosynthetically, we needed to enantioselectively protect one hydroxyl group in **5**. Therefore, we performed the desymmetrisation reaction using an enzymatic reaction (Kawasaki, et al. 2013). Treatment of diol **5** with lipase

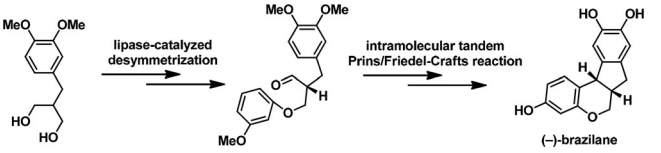
using vinyl acetate as the reagent/solvent at room temperature for 4 h furnished the desired mono-protected alcohol (**4**) in an almost quantitative yield and 96% ee [chiral analysis conditions: OJ-H column, hexane/2-propanol = 4:1 (v/v), 0.5 mL/min, 254 nm]. The absolute configuration of **4** was assumed to be *R* on the basis of Kawasaki's study (Kawasaki, et al. 2013) and the configuration of the final product.

2. Results and discussion

Unfortunately, the next etherification reaction was problematic. None of the desired ether (**3**) was obtained under conventional Mitzunobu reaction conditions using triphenyl phosphine in the presence of diisopropyl azodicarboxylate (DIAP) or diethyl azodicarboxylate (DEAD). According to Li's observations (Huang et al. 2015), 1,1′-(azodicarbonyl)-dipiperidine (ADDP) was used in place of DIAD and DEAD. To our delight, treating **4** and 3-methoxyphenol in the presence of ADDP and Bu_3P in refluxing THF gave the desired ether (**3**) in excellent yield (87%). Subsequently, the acetyl group was readily removed upon treatment with K_2CO_3 in MeOH to release the alcohol group and gave **9** in 89% yield, which smoothly undergoes a Dess-Martin oxidation reaction to give aldehyde **2** in 83% yield.

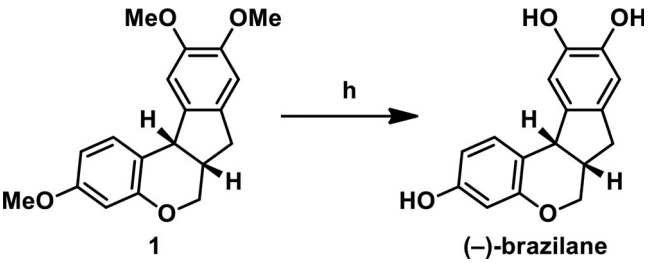
With aldehyde **2** in hand, we next conducted the one pot intramolecular tandem Prins/Friedel-Crafts reaction. We first used the conditions originally employed in the synthesis of brazilin. However, the desired cyclisation product (**1)** was obtained in only 42% yield (Table 1, entry 1). We considered a stronger acid would more readily promote the cyclisation reaction, but unfortunately no obvious changes in the yield of **1** was observed when using trifluoromethanesulfonic acid (TfOH) as the catalyst (0.5 or 1 equiv) (entries 2 and 3). We also increased the amount of trifluoroacetic acid (TFA), and only a slightly lower product yield was obtained (entry 4). Finally, we carried out the cyclisation upon treatment with five equiv of p-toluenesulfonic acid (p-TsOH) at room temperature for 1 h and the desired product was obtained in 51% yield as a single isomer (entry 5), which was identical to our previous study (Huang et al. 2020). To our surprise, compound **1** was found to unstable during our studies on the cyclisation reaction and would decompose even upon storage at −15 °C for a few hours. The low product yield may be attributed to its instability. Therefore, **1** was immediately used in the next demethylation step.

Table 1. Examination of the intramolecular tandem Prins/Friedel-Crafts reaction.



Entry	Reaction conditions	Yield of **9**[a]
1	TFA (0.5 equiv), DCM, rt, 12 h	42%
2	TfOH (0.5 equiv), MeCN, rt, 12 h	42%
3	TfOH (1.0 equiv), MeCN, rt, 1 h	40%
4	TFA (4.0 equiv), DCM, rt, 1 h	38%
5	p-TsOH (5.0 equiv), DCM, rt, 1 h	51%

[a]Yield based upon isolation of the product using silica gel column chromatography.



Scheme 3. *Reagents and conditions*: (h) BBr_3, DCM, -78 °C to r.t., 63%, 96% ee.

Finally, as shown in Scheme 3, the endgame for the synthesis of (–)-brazilane was the removal of the methyl groups on the phenolic hydroxyl groups of intermediate **1** upon treatment with BBr_3 according to a literature procedure (Kim and Kim 2018). (–)-Brazilane was readily obtained in ~63% yield (96% ee) under conventional deprotection conditions using BBr_3, which also indicated that no racemisation occurred during the Prins/Friedel-Crafts cyclisation. The physical and spectral data for the product were identical to those reported in the literature (shown in Table S1 in supplementary material).

3. Experimental

3.1. General

All reactions were carried out under a N_2 atmosphere and with dry solvents unless otherwise noted. They were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (*60 F-254*). Silica gel (200–300 mesh) used for flash column chromatography was supplied by *Qingdao Marine chemical factory* in China. Anhydrous tetrahydrofuran (THF), dichloromethane (DCM) and N, N-dimethyl formamide (DMF) was supplied by *Energy Chemical* in China. Yield refers to that obtained chromatographically and spectroscopically (^1H, ^{13}C NMR), unless otherwise stated. NMR spectra were recorded on a Brucker AVANCE 400 spectrometer (400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR). High-resolution mass spectra were obtained using a Waters Xevo G2-XS QTOF Mass Spectrometer. Chiral HPLC analyses were performed on SHIMADZU LC-10A VP with a UV detector at wavelength $\lambda = 254.0$ nm and OJ-H (15 cm × 0.5 cm) or Waters Acquity Upc2 with a UV detector at wavelength $\lambda = 214.0$ nm and AD-H (15 cm × 0.5 cm) as the stationary phase. Melting points (uncorrected) were determined with an electrothermal capillary melting point apparatus made by *Tianjin optical instrument factory*. Optical rotations were measured on a digital polarimeter in MeOH or CH_2Cl_2 at 25 °C.

3.2. Procedures

3.2.1. Diethyl 2-(3,4-dimethoxybenzyl)malonate (8)

DMAP (0.0872 g, 0.71 mmol), TsCl (0.2720 g, 1.43 mmol) and Et_3N (0.17 mL, 1.19 mmol) were added sequentially to a magnetically stirred solution of **6** (0.2 g, 1.19 mmol) in anhydrous DCM (5 mL) under N_2, The reaction mixture was stirred for 2 h at room

temperature and quenched with H_2O. The mixture was extracted with CH_2Cl_2 (3×6 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide a yellow oily residue, which was purified by flash chromatography on silica gel (EtOAc/PE = 1:10) to give compound **7** as an colourless oil (0.32 g, 83% yield).

To a solution of sodium hydride (60% in mineral oil; 0.0513 g, 1.28 mmol) in anhydrous DMF (2 mL) and THF (2 mL) was added a solution of diethyl malonate (0.24 mL, 1.60 mmol) in THF (2 mL) at 0 °C and the mixture was stirred for 30 min at 0 °C. To this mixture was added an anhydrous THF (2 mL) solution of compound **7** (0.2 g, 1.07 mmol) at 0 °C, followed by stirring at room temperature for 12 h. The mixture was acidified by 2 M HC1 and extracted with EtOAc (3×5 mL). After distillation under reduced pressure and the residue was purified by flash chromatography on silica gel (EtOAc/PE = 1:10) to gave the desired compound **8** as a colourless oil (0.3 g, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.74 (dd, $J = 8.7$, 4.9 Hz, 2H), 6.71 (s, 1H), 4.19-4.09 (m, 4H), 3.83 (s, 3H), 3.82 (s, 3H), 3.60 (dd, $J = 17.0$, 9.2 Hz, 1H), 3.14 (d, $J = 7.8$ Hz, 2H), 1.30-1.14 (m, 6H).

3.2.2. 2-(3,4-Dimethoxybenzyl)propane-1,3-diol (5)

To a suspension of $LiAlH_4$ (0.0053 g, 0.14 mmol) in THF (0.6 mL) was slowly added the solution of **8** (0.0218 g, 0.07 mmol) in THF (0.6 mL) at 0 °C, and the mixture was stirred for 4 h at room temperature. Then the reaction was quenched by addition of methanol (1.0 mL), 15% NaOH aqueous solution (1.0 mL) and water (5.0 mL) at 0 °C. The mixture was acidified by 2 M HCl and extracted with EtOAc (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (MeOH/CH_2Cl_2 = 1:20) to give the compound **5** as a colourless oil (0.014 g, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (d, $J = 9.9$ Hz, 1H), 6.72 (d, $J = 4.9$ Hz, 2H), 3.86 (dd, $J = 3.7$, 1.6 Hz, 6H), 3.83 − 3.78 (m, 2H), 3.7.-3.65 (m, 2H), 2.57 (dd, $J = 7.4$, 2.7 Hz, 2H), 2.35 − 2.12 (m, 2H), 2.07-2.02 (m, 1H), 1.30 − 1.20 (m, 1H).

3.2.3. (R)-2-(3,4-dimethoxybenzyl)-3-hydroxypropyl acetate (4)

Lipase PS (0.5 g) was added to a solution of **5** (0.5 g, 2.21 mmol) in vinyl acetate (20 mL) at room temperature in one portion. The resulting suspension was magnetically stirred at room temperature for 3 h. Then the mixture was filtrated through sand core funnel. The filtrate was condensed in vacuo to provide the crude residue, which was purified using flash silica gel chromatography (EtOAc/PE = 2:1) to provide **4** as a colourless oil. (0.587 g, 99% yield, 96% ee). The ee value of (*R*)-**4** was determined with HPLC {OJ-H, hexane/2-propanol = 4:1 (v/v)}. $[\alpha]_D^{25} = +23.0$ ($c = 1.48$ in CH_2Cl_2);^{1}H NMR (400 MHz, $CDCl_3$): δ 6.77 (d, $J = 8.1$ Hz, 1H), 6.70 (d, $J = 5.73$ Hz, 2H), 4.16 (dd, $J = 11.2$, 4.6 Hz, 1H), 4.06 (dd, $J = 11.2$, 6.5 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.58 (dd, $J = 11.3$, 4.6 Hz, 1H), 3.50 (dd, $J = 11.3$, 6.1 Hz, 1H), 2.59 (m, 3H), 2.07 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.90, 149.02, 147.99, 131.98, 121.16, 112.28, 111.35, 64.16, 62.12, 56.04, 55.97, 42.64, 34.01, 21.07. HRMS (ESI) calcd for $C_{14}H_{21}O_5$ $[M + H]^+$ 269.1389, found 269.1388.

3.2.4. (S)-2-(3,4-dimethoxybenzyl)-3-(3-methoxyphenoxy)propyl acetate (3)

To a stirred solution of 1,1′-(azodicar-bonyl)dipiperidine (0.6827 g, 2.71 mmol) in anhydrous THF (6 mL) was added dropwise Bu_3P (0.77 mL, 3.07 mmol) over 5 min. The resulting mixture was stirred for 0.5 h until the solution turned colorless. At this point, a solution of **4** (0.33 g, 1.23 mmol) in anhydrous THF (6 mL) followed by a solution of 3-methoxyphenol (0.1 mL, 1.00 mmol) in anhydrous THF (6 mL) were added dropwise. Then the reaction was warmed up to 70 °C and stirred for another 12 h at this temperature. The solvent was removed in vacuo, and the residue was rapidly purified on a short silica gel chromatography (EtOAc/PE = 1:5) to produce the desired compound **3** as a colorless oil (0.3620 g, 87% yield). $[\alpha]_D^{25} = -31.1$ ($c = 0.76$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (t, $J = 8.2$ Hz, 1H), 6.78 (d, $J = 6.57$ Hz, 1H), 6.71 (dd, $J = 8.1$, 1.9 Hz, 1H), 6.67 (d, $J = 1.9$ Hz, 1H), 6.52-6.44 (m, 3H), 4.23-4.13(m, 2H), 3.91-3.83 (m, 5H), 3.78 (s, 3H), 3.75 (s, 3H), 2.81-2.70 (m, 2H), 2.42-2.35 (m, 1H), 2.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.23, 161.01, 160.25, 149.00, 147.64, 131.57, 130.07, 121.26,112.42, 111.36,106.85, 106.53, 101.13, 66.65, 64.48,56.05, 55.85, 55.45, 40.15, 34.15, 21.13. HRMS (ESI) calcd for $C_{21}H_{27}O_6$ $[M+H]^+$ 375.1808, found 375.1808.

3.2.5. (R)-2-(3,4-dimethoxybenzyl)-3-(3-methoxyphenoxy)propan-1-ol (9)

Compound **3** (0.2746 g, 0.81 mmol) was dissolved in MeOH (5 mL), and anhydrous K_2CO_3 (0.1683 g, 1.22 mmol) was added. The suspension was stirred at room temperature for 4 h. The reaction was poured into H_2O and extracted with EtOAc (3 × 5 mL). The collected phase was dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography (EtOAc/PE = 1:3) to afford **9** as a a colourless oil (0.2401 g, 89% yield). $[\alpha]_D^{25} = -46.92$ ($c = 0.65$ in CH_2Cl_2);^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (t, $J = 8.2$ Hz, 1H), 6.78 (d, $J = 8.0$ Hz, 1H), 6.72 (dd, $J = 10.4$, 2.2 Hz, 2H), 6.52-6.44 (m, 3H), 3.97 (dd, $J = 9.2$, 4.5 Hz, 1H), 3.91 (dd, $J = 9.2$, 5.9 Hz, 1H), 3.84 (s, 3H), 3.80-3.71 (m, 8H), 2.74 (d, $J = 7.0$ Hz, 2H), 2.29-2.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.97, 160.17, 148.96, 147.51, 132.25, 130.08, 121.17, 112.40, 111.31, 106.85, 106.59, 101.09, 68.36, 63.88, 56.02, 55.84, 55.42, 42.90, 34.01. HRMS (ESI) calcd for $C_{19}H_{25}O_5$ $[M+H]^+$ 333.1702, found 333.1702.

3.2.6. (6 ar,11bR)-3,9,10-trimethoxy-6,6a,7,11b-tetrahydroindeno[2,1-c]chromene (1)

To a stirred solution of **9** (0.1484 g, 0.45 mmol) in CH_2Cl_2 (3 mL), $NaHCO_3$ (0.1313 g, 1.56 mmol) and Dess-Martin periodinane (0.38 g, 0.9 mmol) was added. The reaction was stirred for 3 h at room temperature. Then hexane was added, and the mixture was washed with CH_2Cl_2 (3 × 5 mL). The insoluble material was removed by filtration. The solution was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (EtOAc/hexane = 1:3) to give (0.1224 g, 83% yield) of the compound **2**, which was then subjected to the next cyclisation immediately.p-toluenesulfonic acid (1.35 g, 7.11 mmol) was added to the solution of **2** (0.47 g, 1.42 mmol) in CH_2Cl_2 (6 mL) at room temperature. The mixture was then stirred for 1 h at room temperature and quenched with saturated aq. $NaHCO_3$ (2 mL). The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and washed with brine. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Compound **1** was obtained as a white solid (0.24 g, 51% yield) after silica gel flash chromatography (EtOAc/PE =

1:10). mp: 55.2-56.6 °C . $[\alpha]_D^{25} = -131.2$ ($c = 0.48$ in CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, $J = 8.5$ Hz, 1H), 6.87 (s, 1H), 6.77 (s, 1H), 6.60 (dd, $J = 8.4$, 2.6 Hz, 1H), 6.43 (d, $J = 2.5$ Hz, 1H), 4.23 (d, $J = 6.5$ Hz, 1H), 4.13 (dd, $J = 10.9$, 4.4 Hz, 1H), 3.87 − 3.84 (m, 6H), 3.77 (s, 3H), 3.63 (t, $J = 10.6$ Hz, 1H), 3.18 (dd, $J = 15.7$, 7.2 Hz, 1H), 2.92 (tdd, $J = 6.4$, 4.2, 2.0 Hz, 1H), 2.60 (dd, $J = 15.7$, 2.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.31, 155.73, 148.99, 148.38, 137.45, 132.80, 130.87, 116.08, 108.56, 108.15, 108.01, 102.00, 67.04, 56.29, 56.24, 55.50, 43.40, 37.07, 34.22, 29.91. HRMS (ESI) calcd for $C_{19}H_{21}O_4$ $[M + H]^+$ 313.1440, found 313.1440.

3.2.7. (–)-Brazilane

To a solution of compound **1** (0.1 g) in CH_2Cl_2 was dropwise added BBr_3 (1 M in CH_2Cl_2, 1.53 mL, 1.53 mmol) at −78 °C. After being stirred at −78 °C for 2 h, the reaction mixture was stirred at room temperature for another 5 h. The mixture was quenched with H_2O and extracted with EtOAc (3 × 10 mL) . The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel flash chromatography (EtOAc/PE/CH_2Cl_2= 1:1:1) to give (–)-brazilane (0.055 g, 63% yield, 96% ee) as a red solid. The ee value was determined with HPLC {AD-H column, hexane/MeOH = 20:3 (v/v), 0.5 mL/min, 214 nm} . mp: 157-159 °C. $[\alpha]_D^{25} = -81.3$ ($c = 0.17$ in MeOH); ^1H NMR (400 MHz, CD_3OD): δ 7.16 (d, $J = 8.3$ Hz, 1H), 6.73 (s, 1H), 6.60 (s, 1H), 6.40 (dd, $J = 8.3$, 2.5 Hz, 1H), 6.20 (d, $J = 2.5$ Hz, 1H), 4.07-3.98 (m, 2H), 3.45 (t, $J = 10.6$ Hz, 1H), 3.02 (dd, $J = 15.6$, 7.1 Hz, 1H), 2.77-2.71 (m, 1H), 2.44 (dd, $J = 15.6$, 1.9 Hz, 1H). ^{13}C NMR (100 MHz, MeOD): δ 157.73, 156.79, 145.47, 145.20, 138.37, 133.25, 132.16, 116.76, 112.98, 112.63, 109.67, 104.33, 67.88, 44.28, 38.43, 34.63. HRMS (ESI) calcd for $C_{16}H_{15}O_4$ $[M + H]^+$ 271.0970, found 271.0968.

4. Conclusions

In conclusion, we have accomplished an efficient synthetic route toward the stereoselective total synthesis of (–)-brazilane, in which a lipase-catalyzed desymmetrisation reaction to prepare a chiral primary alcohol using vinyl acetate was the key step. This chiral center controlled the subsequent one-pot intramolecular tandem Prins/Friedel-Crafts reaction to construct the *cis*-fused chromane and indane framework. This approach showed an alternative synthetic strategy towards brazilane, especially for similar compounds containing the *cis*-fused chromane and indane framework. Further studies on the applications of this approach to natural products and pharmaceuticals are in currently in progress in our laboratory and will be disclosed in due course.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the National Natural Science Foundation of China (No. 82003810, 21062088), Natural Science Foundation of Jiangxi Province (No. 20161BAB204189) and Research funds for outstanding doctors from Shanxi provincial finance.

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