STRAIGHTFORWARD AND FACILE SYNTHESIS OF A BIOACTIVE COMPONENT FROM ZINGIBER CASSUMUNAR ROXB.

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GRAPHICAL ABSTRACT

Abstract Straightforward and facile synthesis of a bioactive component A from Zingiber cassumunar Roxb. is described. The phenylbutenoid dimer A was reported to possess anti-inflammatory and cytotoxic activities. The optically active cyclohexene ring fragment was obtained via the highly diastereo- and enantioselective Diels–Alder reaction of chiral acryloyloxazolidinones (1a and 1b) and 1-(4-hydroxy-3-methoxyphenyl)butadiene (2). The enantiomeric excess of Diels–Alder adducts 3a and 3b were determined via high-performance liquid chromatotography of the corresponding bis-acetate (6). The greatest enantiomeric excess (99.9% ee) was obtained when the 4-phenyloxazolidin-2-one (1a) chiral auxiliary was used in combination with TiCl4. The optically pure bioactive compound A was prepared from the optically active Diels–Alder adduct (3a) in two additional steps.

Keywords Chiral auxiliaries; Diels–Alder reaction; enantioselective synthesis; phenylbutenoid dimer

INTRODUCTION

Several bioactive components were isolated from Zingiber cassumunar Roxb., the tropical ginger widely distributed in Southeast Asia.1,2 The extracted oil of this herb was known as Plai oil in Thailand and is used as massage oil by
massage therapists. Among isolated bioactive components, (±)-trans-3-(4-hydroxy-3-methoxyphenyl)-4-((E)-3,4-dimethoxystyrly)cyclohex-1-ene (racemic mixture of A, Fig. 1), was reported to possess both anti-inflammatory and cytotoxic activities in recent studies.[2,3] Therefore, it was interesting for medicinal chemists to rebuild the structure and improve bioactivity of the phenylbutenoid dimer A.

The Diels–Alder (DA) reaction is one of the most powerful methods for constructing cyclohexene ring systems and has been used as a key step in many notable syntheses of complex natural products. Evans’s oxazolidinone chiral auxiliaries, which were initially developed for aldol and alkylation reactions, have found extensive applications in organic synthesis and have continually been employed over the past 20 years.[4,5] The phenylbutenoid dimer A can be synthesized via DA reaction following the strategy. The cyclohexene ring fragment of the target compound A with two vicinal stereogenic centers can be efficiently constructed by DA reaction between an appropriately substituted diene and an unsaturated carbonyl analog. Dienophiles with chiral auxiliaries can be utilized to obtain optically active DA adducts.

In our ongoing research toward discovery of potential drug candidates with anti-inflammatory activity from oriental medicinal herbs, we were interested in this compound. However, because of difficulties in isolation and purification, development of an efficient total synthesis of the compound A was needed not only to obtain sufficient amount of sample for in vivo tests but also to synthesize a number of analogs for conducting structure–activity relationship study (SARs). In addition, development of an asymmetric synthetic method for the bioactive substance was also necessary because optical isomers of chiral compounds usually showed different biological activity. Herein we report a straightforward and facile synthesis of an optically active phenylbutenoid dimer A.

RESULTS AND DISCUSSION

Chiral acryloyloxoazolidinones (1a and 1b) were prepared from the corresponding commercially available oxazolidinones and acrylic acid and used as the dienophiles for the DA reactions. As the diene for DA reaction, 1-(4-hydroxy-3-methoxy)phenylbutadiene (2) was prepared from commercial vanillin in two steps. As outlined in Scheme 1, reactions of chiral oxazolidinones with acrylic acid, pivaloyl chloride, and Et₃N in tetrahydrofuran (THF) produced 4-phenyl (1a, 86%) and 4-isopropyl (1b, 56%) acryloyl analogs.[6] Zinc-mediated allylation of vanillin, followed by dehydration reaction in the presence of p-toluenesulfonic acid, gave the diene (2) in 52% yield. The asymmetric DA reaction between the dienophile (1a) and diene (2) with Et₂AlCl as
the Lewis acid yielded a single DA adduct (3a) in 60% yields and 93.8% enantiomeric excess (Table 1, entry 1). However, the desired product was not detected when 1b was used under the same condition. Excellent yields and greater enantiomeric excesses were obtained when TiCl4 was used as Lewis acid (entry 3 and 4). The products 3a and 3b were identified as 3,4-cis stereoisomers based on the coupling constant values in 1H NMR data. Reduction of the DA adducts afforded aldehyde 4 in 74% yield. The reaction in Schlosser conditions between aldehyde 4 and (3,4-dimethoxybenzyl)triphenylphosphonium bromide at −20°C to reflux yielded the optically active compound A as a single diastereomer. Thus, optically active trans-3-(4-hydroxy-3-methoxyphenyl)-4-(((E)-3,4-dimethoxystyryl)cyclohex-1-ene (A) was successfully synthesized via chiral DA reaction as the key step as described in Scheme 1. Our procedure provided the target molecule (A) with excellent enantiomeric excess (ee) in two steps from the DA adducts (3a and 3b). The synthesis of optically active phenylbutenoid dimers via a similar method has been reported. However, their method required a much longer sequence (five steps from the DA adducts) to obtain the optically active phenylbutenoid dimmers with the natural trans stereochemistry, produced a by-product with Z-stereochemistry during Horner–Wadsworth–Emmons condensation, and did not provide detailed conditions and data for determining ee. Our results provided detailed experimental conditions for complete separation of the peaks in high-performance liquid chromatographic (HPLC) analysis with a chiral column.

### Table 1. Results of the asymmetric Diels–Alder reactions

| Entry | Dienophile | Lewis acid | Product | Yield (%) | ee (%) |
|-------|------------|------------|---------|-----------|--------|
| 1     | 1a         | Et2AlCl    | 3a      | 60        | 93.8   |
| 2     | 1b         | Et2AlCl    | ND      | ND        | ND     |
| 3     | 1b         | TiCl4      | 3b      | 95        | 97.1   |
| 4     | 1a         | TiCl4      | 3a      | 92        | 99.9   |

*aReaction conditions: dienophile 1 (1.0 equiv), diene 2 (1.5 equiv), Et2AlCl (1.0 equiv), CH2Cl2, −78°C, 5 h; or dienophile 1 (1.0 equiv), diene 2 (1.5 equiv), TiCl4 (1.0 equiv), CH2Cl2, −20°C, 2 h.*

*bIsolated yield after chromatography.

*cBased on the chiral HPLC analysis of diacetate 6.

*dNot detected.
Enantiomeric excesses of the DA adducts 3\(\text{a}\) and 3\(\text{b}\) were determined by HPLC analysis on a chiral column (Shimazu Chiracel OD, 250 mm × 4.6 mm i.d.) in comparison with racemic products using hexane/EtOH/i-PrOH/t-BuOH(480/2/1/1) as the mobile phase. Determination of ee by HPLC failed because the DA adducts (3\(\text{a}\), 3\(\text{b}\)) and the compound 4 did not afford clean baseline separation of the peaks. Reduction of the DA adducts afforded the corresponding alcohol (5). However, complete chiral separation in HPLC analysis with the alcohol (5) was also not successful. Therefore, we converted the alcohol to its acetate (6) as described in Scheme 2. The compound 6 gave spectra with cleanly separated baseline of two peaks on HPLC analysis (Table 1).

It was determined that the enantiomeric excesses of the DA reactions were dependent on both the chiral auxiliary and Lewis acid. The DA reaction between the dienophile with the 4-phenyloxazolidin-2-one chiral auxiliary (1\(\text{a}\)) and TiCl\(_4\) gave best result as shown in Table 1 (>99.9% ee). Inhibitory activities of nitric oxide (NO) production from lipopolysaccharide (LPS)-treated BV2 cells of optically active compound A and racemic compound A were evaluated. These data will be published in other scientific journals soon.

**EXPERIMENTAL**

All chemicals were obtained from commercial suppliers and used without further purification. All solvents used for reactions were freshly distilled from proper dehydrating agent under nitrogen gas. All solvents used for chromatography were purchased and directly applied without further purification. \(^1\)H NMR spectra were recorded on a Bruker Avance 300 (300-MHz) and Bruker DPX 400 (400-MHz) spectrometers. Chemical shifts are reported in parts per million (ppm) downfield relative to tetramethylsilane (TMS) as an internal standard. Peak splitting patterns are abbreviated as m (multiplet), s (singlet), bs (broad singlet), d (doublet), bd (broad doublet), t (triplet), dd (doublet of doublets), and ddd (doublet of double doublet). \(^1\)H NMR spectra were recorded on a Bruker DPX 400 (100-MHz) spectrometer, fully decoupled, and chemical shifts are reported in parts per million (ppm) downfield relative to TMS as an internal standard. HPLC was carried out on a Wellchrom HPLC system (Knauer, Germany) equipped with a Shimazu Chiracel OD (250 mm × 4.6 mm i.d.). Optical rotation data were collected by a Jasco DIP-1000 digital polarimeter. Mass spectra were recorded on a Voyager DESTR MALDI-TOF mass spectrometer. Melting points were recorded on a Fisher-Johns microscopic-scale melting-point apparatus.
Analytical thin-layer chromatography (TLC) was performed using commercial glass plates with silica gel 60F254 purchased from Merck. Chromatographic purification was carried out by flash chromatography using Kieselgel 60 (230–400 mesh, Merck). (3,4-Dimethoxybenzyl)triphenylphosphonium bromide was prepared according to the literature method.\[11\]

**Synthesis of (S)-3-((1R,2S)-2-(4-Hydroxy-3-methoxyphenyl)cyclohex-3-ene carbonyl)-4-phenyloxazolidin-2-one (3a)**

To a solution of 1a (0.15 g, 0.69 mmol) in CH$_2$Cl$_2$ (7 mL) were added Et$_2$AlCl (0.69 mL, 1 M in CH$_2$Cl$_2$) dropwise and 2 (0.16 g, 0.91 mmol) in CH$_2$Cl$_2$ (3 mL) at $-78^\circ$C. The reaction was stirred for 5 h, then warmed to 0°C, quenched with 1 N HCl (2 mL), and extracted with CH$_2$Cl$_2$ (30 mL). The organic layer was washed with saturated NaHCO$_3$ (10 mL) and brine (10 mL), dried over mgSO$_4$, filtered, and evaporated. The residue was purified by column chromatography (hexane–cetone, 4:1) to give 3a (0.16 g, 60%) as a white solid. Mp 148–150°C; $[\alpha]^{14}_D$ +278.1 (c 0.1, CHCl$_3$).

$^1$HNMR (400 MHz, CDCl$_3$): $\delta$ = 7.35–7.10 (m, 5H, phenyl), 6.52 (d, $J$ = 1.9 Hz, 1H, ArH), 6.2–6.15 (d, $J$ = 8.1 Hz, 1H, ArH), 5.88 (m, 1H, vinyl), 5.70 (m, 1H, vinyl), 5.37 (s, 1H, OH), 5.32 (d, $J$ = 8.8, 3.8 Hz, 1H, H-4), 4.63 (t, $J$ = 8.8 Hz, 1H, H-5), 4.32 (dd, $J$ = 8.8, 3.8 Hz, 1H, H-5), 4.12-3.97 (m, 2H, C$_2$HCH$_2$C=O), 3.62 (s, 3H, OCH$_3$), 2.30–1.70 (m, 4H, C$_2$H$_2$). $^{13}$CNMR (100 MHz, CDCl$_3$): $\delta$ = 173.8, 153.9, 146.2, 144.5, 139.0, 132.4, 129.3, 129.2, 128.9, 127.4, 127.1, 122.4, 114.0, 112.0, 70.3, 58.2, 56.1, 44.0, 42.0, 24.3, 21.2. MS (MALDI-TOF): m/z [M + Na]$^+$ 416.1546.

**Compound 3a**

Following a similar procedure using TiCl$_4$ as Lewis acid at $-20^\circ$C, 3a was obtained as a white solid (92%). $[\alpha]^{14}_D$ +403.2 (c 0.1, CHCl$_3$).

**Supporting Information**

Full experimental detail, $^1$H and $^{13}$C NMR spectra, MS data, and HPLC traces are available for this article.

**CONCLUSION**

In conclusion, a straightforward and facile synthetic procedure for the synthesis of optically active, naturally occurring, phenylbutenoid dimer A was developed via highly diastereo- and enantioselective Diels–Alder reaction as the key step. The greater enantiomeric excesses of reactions with TiCl$_4$ catalyst may due to formation of the tight titanium complex instead of the aluminum complex. Our present method enables us to efficiently generate sufficient amounts of (+)-trans-3-(4-hydroxy-3-methoxyphenyl)-4-((E)-3,4-dimethoxystyryl)cyclohex-1-ene (A) in very few synthetic operations (two steps from the DA adducts) without any unnecessary steps.
(protection–deprotection of phenol group), with extremely high stereoselectivity (single product as cis form) and enantiomeric excess (>99.9%). Therefore, our synthetic procedure can be efficiently applied to SAR studies of compound A.

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SUPPLEMENTAL MATERIAL

Supplemental data for this article can be accessed on the publisher’s website.

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