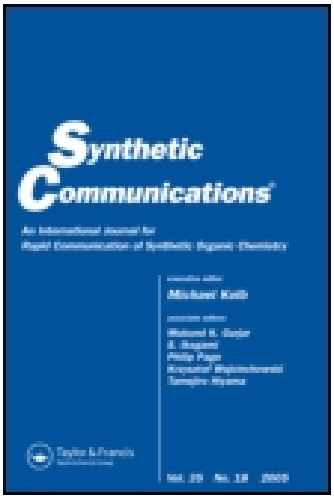

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Accepted author version posted online: 04 Dec 2013.Published online: 28 Mar 2014.

To cite this article: Yuanying Fang , Zunhua Yang & Haeil Park (2014) Straightforward and Facile Synthesis of a Bioactive Component from Zingiber cassumunar Roxb., Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 44:9, 1212-1217, DOI: 10.1080/00397911.2013.846380

To link to this article: http://dx.doi.org/10.1080/00397911.2013.846380

Synthetic Communications®, 44: 1212–1217, 2014

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2013.846380

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

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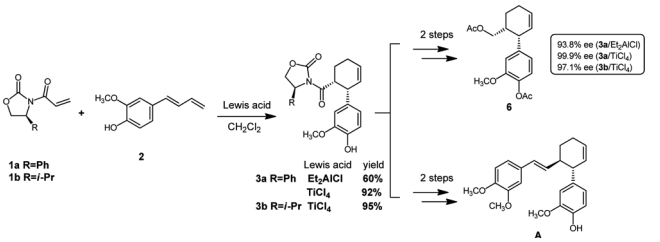
GRAPHICAL ABSTRACT



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

Received May 28, 2013.
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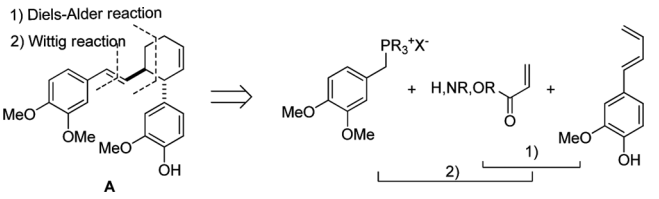


Figure 1. Retrosynthetic analysis of the phenylbutnoid dimer **A.**

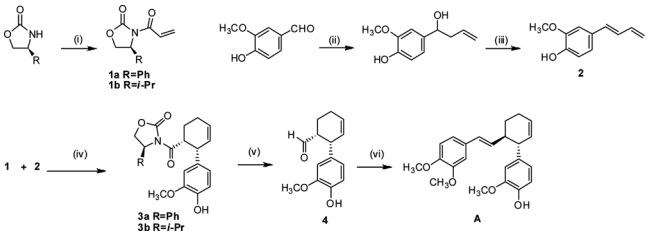
massage therapists. Among isolated bioactive components, (±)-*trans*-3- (4-hydroxy-3-methoxyphenyl)-4-((*E*)-3,4-dimethoxystyryl)cyclohex-1-ene (racemic mixture of **A**, Fig. 1), was reported to possess both anti-inflammatory and cytotoxic activities in recent studies.[2,3] Therefore, it was interesting 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 acryloyloxazolidinones (**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 Et_3N 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 Et_2AlCl as



Scheme 1. Reagents and conditions: (i) acrylic acid, pivaloyl chloride, LiCl, Et_3N, THF, –20 °C to rt, 4 h, 86% (for **1a**), 56% (for **1b**); (ii) allyl bromide, Zn(dust), aqueous NH_4Cl solution, THF, 0 °C, 0.5 h; (iii) PTSA, toluene, reflux, 1 h, 52% in two steps; (iv) Et_2AlCl, CH_2Cl_2, –78 °C, 5 h, 60% (for **3a**); $TiCl_4$, CH_2Cl_2, –20 °C, 2 h, 95% (for **3b**), 92% (for **3a**); (v) DIBAL-H, CH_2Cl_2, –78 °C, 2 h, 74%; (vi) (3,4-dimethoxybenzyl) triphenylphosphonium bromide, n-BuLi, toluene, –20 °C to reflux, 41%.

the Lewis acid yielded a single DA adduct (**3a**) in 60% yields and 93.8% enantiomeric excess (Table 1, entry 1).[5] However, the desired product was not detected when **1b** was used under the same condition. Excellent yields and greater enantiomeric excesses were obtained when $TiCl_4$ was used as Lewis acid (entry 3 and 4).[7] The products **3a** and **3b** were identified as 3,4-*cis* stereoisomers based on the coupling constant values in ^1H NMR data.[8,9] 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.[10] 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[a]

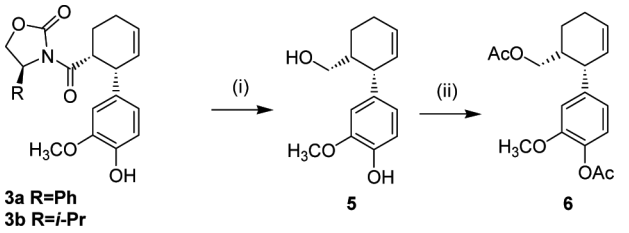
Entry	Dienophile	Lewis acid	Product	Yield (%)[b]	*ee* (%)[c]
1	**1a**	Et_2AlCl	**3a**	60	93.8
2	**1b**	Et_2AlCl	ND[d]	ND	ND
3	**1b**	$TiCl_4$	**3b**	95	97.1
4	**1a**	$TiCl_4$	**3a**	92	99.9

[a]Reaction conditions: dienophile **1** (1.0 equiv), diene **2** (1.5 equiv), Et_2AlCl (1.0 equiv), CH_2Cl_2, –78 °C, 5 h; or dienophile **1** (1.0 equiv), diene **2** (1.5 equiv), $TiCl_4$ (1.0 equiv), CH_2Cl_2, –20 °C, 2 h.

[b]Isolated yield after chromatography.

[c]Based on the chiral HPLC analysis of diacetate **6**.

[d]Not detected.



Scheme 2. Reagents and conditions: (i) LAH, THF, 0 °C to rt, 4 h, 63%; (ii) Ac_2O, pyridine, CH_2Cl_2, 0 °C to rt, 2 h, 78%.

Enantiomeric excesses of the DA adducts **3a** and **3b** 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 (**3a, 3b**) 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 (**1a**) 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}HNMR 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). ^{13}CNMR 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 DE STR 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 $60F_{254}$ 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-enecarbonyl)-4-phenyloxazolidin-2-one (3a)

To a solution of **1a** (0.15 g, 0.69 mmol) in CH_2Cl_2 (7 mL) were added Et_2AlCl (0.69 mL, 1 m in CH_2Cl_2) dropwise and **2** (0.16 g, 0.91 mmol) in CH_2Cl_2 (3 mL) at −78 °C.The reaction was stirred for 5 h, then warmed to 0 °C, quenched with 1 N HCl (2 mL), and extracted with CH_2Cl_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, $CDCl_3$): δ = 7.35–7.10 (m, 5H, phenyl), 6.52 (d, *J* = 1.9 Hz, 1H, ArH), 6.2™, *J* = 8.1 Hz, 1H, ArH), 6.15 (dd, *J* = 8.1, 1.9 Hz, 1H, ArH), 5.88 (m, 1H, vinyl), 5.70 (m, 1H, vinyl), 5.37 (s, 1H, OH), 5.32 (dd, *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*H*C*H*C=O), 3.62 (s, 3H, OCH_3), 2.30–1.70 (m, 4H, CH_2CH_2). ^{13}CNMR (100 mHz, CDCl3): δ = 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 °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**.

ACKNOWLEDGMENT

The authors thank New Drug Development Research Institute and Central Laboratory of Kangwon National University for the use of analytical instruments and bioassay facilities.

FUNDING

This research was supported by University–Industry Cooperation Foundation of Kangwon National University (Foreign Post-doc Invitation Program).

SUPPLEMENTAL MATERIAL

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

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