AN EFFICIENT SYNTHESIS OF (±)-Cycloillicinone

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GRAPHICAL ABSTRACT

Abstract An efficient synthesis of (±)-cycloillicinone was accomplished in five steps from sesamol. The title compound was obtained via a biomimetic Diels–Alder cycloaddition between illicinone A and β-trans-ocimene as the key step.

Keywords Diels–Alder reaction; illicinone; sesamol; β-trans-ocimene

INTRODUCTION

Cycloillicinone 1 was originally isolated from the toxic plant Illicium anisatum in 2011.[1] This compound belongs to the class of phytoquinoids known for their antitumor and cytotoxic activities.[2–4] The structure of 1, which features a highly substituted cyclohexenone and a methylenedioxy function in a non-aromatic setting, was elucidated on the basis of nuclear Overhauser effect spectroscopy (NOE), correlation spectroscopy (1H-1H-COSY), heteronuclear multiple quantum correlation (HMQC), and heteronuclear multiple bond correlation (HMBC) experiments.[1] Two years later, Shen and colleagues reported the isolation of illicarborene A, an enantiomer of 1 from the Illicium arborescens and its structure was elucidated by extensive NMR analysis and chemical degradation.[3] Acid hydrolysis of illicarborene A leads to illicarborene B 2.[3] The absolute configurations of 1 and illicarborene A, however, have not been fully defined due to the lack of circular dichroism or x-ray crystallographic data (Fig. 1).
Prompted by the unique structure of cycloillicinone 1 and its potential as lead compound for developing new antitumor drugs, we decided to undertake its total synthesis. Our retrosynthetic analysis assumed that the natural product originates from sesamol and \( \beta \)-trans-ocimene (Scheme 1). A biosynthetic pathway was postulated by Fukuyama et al., featuring a Diels–Alder reaction between \( \beta \)-trans-ocimene and illicinone A. The latter exists as a pair of enantiomers in nature.

RESULTS AND DISCUSSION

At first, we obtained illicinone A 7 from sesamol 3 through a four-step reaction as described in the literature. We began the synthesis with the \( O \)-allylation of sesamol 3. Claisen rearrangement of allyl ether 4 under thermal conditions provided phenol 5 in 90% yield. Prenylation of phenol 5 afforded natural product illicinole 6.

Subsequently, methylaluminum bis(4-bromo-2,6-di-tert-butylphenoxide) (MABR) promoted rearrangement of illicinole 6 cleanly to give the racemic illicinone A 7 in 65% yield; see Scheme 2.

With dienophile 7 in hand, we then performed the Diels–Alder cycloaddition with \( \beta \)-trans-ocimene. Several screenings of catalysts (\( \text{TiCl}_4 \), \( \text{Et}_2\text{AlCl} \), \( \text{AlBr}_3 \), \( \text{BF}_3 \cdot \text{Et}_2\text{O} \), \( \text{AlCl}_3 \), \( \text{ZnCl}_2 \), \( \text{TfOH} \), and \( \text{S}(-)\text{-o-tolyl-CBS-oxazaborolidine} \)) showed trifluoromethanesulfonimide activated CBS-oxazaborolidine to be the best choice for catalyst to produce 1 as the single adduct in a 55% yield (entry 11, Table 1). Diels–Alder cycloaddition between 7 and \( \beta \)-trans-ocimene under thermal conditions afforded 1 as that of CBS-oxazaborolidine (entry 1, Table 1). However, the reaction time was long (24 h) and several undesired side products 5, 6, and 8 arising from rearrangement of illicinone A 7 were also obtained. The cycloaddition reaction using strong Lewis acids (i.e., \( \text{TiCl}_4 \), \( \text{Et}_2\text{AlCl} \), \( \text{AlBr}_3 \)) has resulted in sample...
decomposition (entries 14–16, Table 1). The cycloaddition reaction catalyzed by ZnCl₂ was clean but the rate of reaction was significantly slower (entries 5 and 6, Table 1). In all cases, \((\text{C}_6\text{H}_5)\)-cycloillicinone 1 was isolated as the only Diels–Alder adduct. To our surprise, no other regioisomer or diastereomer was observed.

**Scheme 2.** Reagents and conditions: (a) allyl bromide (1.1 eq), K₂CO₃ (10 eq), acetone, pressure tube, 60 °C, 8 h, 95%; (b) DMF, 190 °C, 12 h, 90%; (c) prenyl bromide (1.1 eq), K₂CO₃ (3 eq), acetone (5 mL), pressure tube, 60 °C, 15 h, 80%; (d) MABR (2 eq), CH₂Cl₂ (5 mL), −78 °C, 2 h, 65%; (e) \(\beta\text{-trans-ocimene}\) (5 eq). For conditions see Table 1.

**Table 1.** Diels–Alder reaction of illicinone A 7 and \(\beta\text{-trans-ocimene}\)

| Entry | Conditions* | Amount (mol %) | Solvent | Temp. (°C) | Time (h) | Isolated yield (%) \(\pm\) 1  5  6  8 |
|-------|-------------|----------------|---------|------------|---------|-----------------|
| 1     | Thermal condition in pressure tube | — | Toluene | 130 | 24 | 47 35 10 2 |
| 2     | — | — | Toluene | rt | 2 | — — — — |
| 3     | CF₃SO₂H | 20 | CH₂Cl₂ | −20°C | 2 | 16 55 10 8 |
| 4     | CF₃SO₂H | 20 | Toluene | −20°C | 2 | 15 50 10 5 |
| 5     | ZnCl₂ | 20 | CH₂Cl₂ | −20°C | 36 | 25 — — — |
| 6     | ZnCl₂ | 20 | Toluene | −20°C | 36 | 20 — — — |
| 7     | AlCl₃ | 20 | CH₂Cl₂ | −20°C | 2 | 29 45 5 2 |
| 8     | AlCl₃ | 20 | Toluene | −20°C | 2 | 29 45 5 3 |
| 9     | BF₃·Et₂O | 20 | CH₂Cl₂ | −20°C | 2 | 30 35 10 15 |
| 10    | BF₃·Et₂O | 20 | Toluene | −20°C | 2 | 30 35 10 15 |
| 11    | (S)-(−)-\(\text{o-Tolyl-CBS-oxazaborolidine,}\) TF₂NH activated | 20 | CH₂Cl₂ | −40°C | 8 | 55 — — — |
| 12    | (S)-(−)-\(\text{o-Tolyl-CBS-oxazaborolidine,}\) TF₂NH activated | 20 | Toluene | −40°C | 8 | 50 — — — |
| 13    | (S)-(−)-\(\text{o-Tolyl-CBS-oxazaborolidine,}\) TF₂NH activated | 20 | THF | −40°C | 8 | 15 — — — |
| 14    | TiCl₄ | 20 | CH₂Cl₂ | −20°C | 2 | — — — — |
| 15    | AlBr₃ | 20 | CH₂Cl₂ | −20°C | 2 | — — — — |
| 16    | Et₂AlCl | 20 | CH₂Cl₂ | −20°C | 2 | — — — — |

*aReaction conditions: dienophile 7 (1.0 equiv), diene \(\beta\text{-trans-ocimene}\) (4 equiv), catalyst 20 mol%, solvent 4 mL/mmol.

bIsolated yield after chromatography.
The exclusive formation of adduct 1 warrants further mechanistic studies to be conducted on the cycloaddition reaction of sterically substituted cyclohexenone dienophile 7. Spectral data for the (±)-cycloillicinone 1 synthesized were in agreement with those reported by Fukuyama et al. and Shen et al. for the natural product. The relative stereochemistry of 1 was confirmed by nuclear Overhauser effect spectroscopy (NOESY) (Fig. 2). The NOE correlations of H-3 with H-7 and H-10 and that of H-7 with H-10 indicated that the allyl group at C-2 and the prenyl group at C-4 were in a cis relationship. On the other hand, correlations of H-20 with H-7 and H-3 indicated that the allyl group at C-2 and the prenyl group at C-20 were in a trans arrangement.

Finally, separation of racemic cycloillicinone 1 using the Daicel Chiralpak IC chiral column (150 mm × 4.6 mm × 5 µm) (mobile phase consisted of n-hexane/isopropanol, 100:0; 92:8; 80:20, v/v; flow rate of 1.0 mL/min; UV detector wavelength was set as 254 nm) was successful. Separation of (±)-1 by using a semi-preparative column (250 mm × 10 mm × 5 µm) is underway.

In conclusion, we have synthesised (±)-cycloillicinone from the commercially available sesamol in 5 steps with a 24% overall yield. This procedure provide a practical synthesis of (±)-cycloillicinone. Efforts to complete an asymmetric synthesis and to determine the absolute configuration of cycloillicinone are in progress.

EXPERIMENTAL

All chemicals were obtained from commercial suppliers and used without further purification. Anhydrous tetrahydrofuran (THF) was distilled from sodium/benzophenone before use. Anhydrous dichloromethane was distilled from calcium hydride under positive pressure of nitrogen. The other anhydrous solvents and reagents were purchased from Aldrich or Fisher. All reactions were carried out under a nitrogen atmosphere unless specified. The NMR spectra were obtained using a Jeol ECA 400 (400 MHz) NMR spectrometer with tetramethylsilane (TMS) as the internal standard. All chemical shifts are reported in parts per million (ppm). Mass spectra were recorded on an Agilent G6530A Accurate-Mass Q-TOF LC/MS spectrometer, and high-performance liquid chromatography (HPLC) was carried out on a Waters HPLC system equipped with a Daicel Chiralpak IC chiral column (150 mm × 4.6 mm × 5 µm). Analytical thin-layer chromatography (TLC) was carried out on Merck precoated aluminum silica-gel sheets (Kieselgel 60 F-254). Column chromatography was done with silica gel 60 (230–400 mesh) from Merck. All target compounds were characterized by $^1$H, $^{13}$C, 2D NMR and MS analysis.
Trifluoromethanesulfonimide (0.5 M solution in CH$_2$Cl$_2$, freshly prepared, 400 µL, 0.2 mmol) was added dropwise to a solution of (S)-(–)-o-tolyl-CBS-oxazaborolidine (0.5 M solution in toluene, 400 µL, 0.2 mmol) at –25 °C. After 10 min at –25 °C, a colorless homogeneous catalyst solution was formed. A solution of illicinone A (7) (246 mg, 1 mmol) in CH$_2$Cl$_2$ (4.0 mL) and β-trans-ocimene (666 µL, 544 mg, 4 mmol) were added successively at –78 °C. The reaction mixture was stirred for 2 h at –40 °C and then another 8 h at room temperature before it was quenched by addition of 20 µL of Et$_3$N. The solvent was removed by rotary evaporation, and the residue was purified by silica-gel chromatography (gradient elution with 10–20% EtOAc–hexanes) to afford adduct (1) (210 mg, 55%). Colorless oil. $^1$H NMR (CDCl$_3$-d$_1$, 400 MHz): δ 5.85 (m, 1H), 5.59 (d, $J = 5.0$, 1H), 5.55 (s, 1H)*, 5.41 (s, 1H), 5.16 (brs, 1H), 5.04 (d, $J = 17.1$, 1H), 5.00 (d, $J = 9.5$, 1H), 5.00 (m, 1H), 2.52 (dd, $J = 14.0$, 8.0, 1H), 2.51 (m, 1H), 2.49 (dd, $J = 15.4$, 5.8, 1H), 2.36 (dd, $J = 13.9$, 6.8, 1H), 2.23 (m, 1H), 2.17 (dd, $J = 15.6$, 7.6, 1H), 2.12 (dd, $J = 10.2$, 4.6, 1H), 1.95 (m, 1H)*, 1.72 (s, 3H), 1.68 (s, 3H), 1.63 (s, 3H), 1.57 (s, 3H), 1.50 (s, 3H); $^{13}$C NMR (CDCl$_3$-d$_1$, 100 MHz): δ 201.5, 172.6, 142.1, 136.4, 134.9, 132.1, 123.4, 121.6, 118.0, 116.6, 99.4, 97.9, 83.9, 53.9, 51.3, 45.2, 40.8, 37.2, 29.7, 25.9, 25.6, 24.3, 24.0, 18.3, 17.8 (*overlapped); HRMS (ESI) calcd. for C$_{25}$H$_{35}$O$_3$ [M+H]$^+$ = 383.2581. Found 383.2585.

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**SUPPORTING INFORMATION**

Full experimental details, $^1$H and $^{13}$C NMR data, HPLC chromatogram, and HRMS spectra for this article can be accessed on the publisher’s website.

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