Linderaggrenolides A–N, Oxygen-Conjugated Sesquiterpenoid Dimers from the Roots of *Lindera aggregata*

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**ABSTRACT:** Linderaggrenolides A–N (1–14), 14 new lindenane sesquiterpenoid dimers with oxygen bridges were isolated from the roots of *Lindera aggregata*. Their structures were elucidated on the basis of comprehensive spectroscopic data analysis, with the absolute configurations established by empirical approaches, electronic circular dichroism calculations, and X-ray crystallography. Compounds 8 and 9 were found to exhibit significant transforming growth factor-β (TGF-β) inhibitory activity, with IC_{50} values of 25.91 and 21.52 μM, respectively.

1. INTRODUCTION

Sesquiterpenoid dimers, plausibly biosynthesized via the coupling of two identical or different sesquiterpenoid molecules, are a class of naturally occurring metabolites with C_{30} cores and possess a variety of biological activities including anti-inflammatory, antimalarial, antitumor, and anti-HIV activities. These metabolites can be found in some higher plant families including the *Chloranthaceae*, particularly the genera *Artemisia* and *Ligularia*. The genus *Lindera* belongs to the family *Lauraceae*, comprising approximately 100 species. Among them, *Lindera aggregata* has been used for thousands of years as a traditional Chinese medicine for the treatment of diseases such as rheumatism, chest and abdominal pain, regurgitation, and frequent urination. Phytochemical investigations into this species have revealed the presence of miscellaneous types of natural products such as sesquiterpenoids, alkaloids, flavonoids, lignans, condensed tannins, and cyclopentene-diones. Our previous phytochemical studies on this plant lead to the isolation of two methine- or methylene-bridged sesquiterpenoid trimers possessing a unique C_{46} skeleton, four carbon-bridged disesquiterpenoids with a C_{33} or C_{31} skeleton, and four disesquiterpenoid–geranylbenzofuranone conjugates. The preliminary results showed that the ethanol extract from the roots of *L. aggregata* exhibited the transforming growth factor (TGF)-β inhibitory activity. Motivated by these findings, we performed a thorough phytochemical investigation into the ethanol extract of the roots of *L. aggregata*, resulting in the isolation and identification of 14 new lindenane sesquiterpenoid dimers (1–14) featuring an oxygen bridge (Figure 1). Herein, we presented the isolation, structural characterization, and potential bioactivities of these new sesquiterpenoid dimers.

2. RESULTS AND DISCUSSION

Linderaggrenolide A (1) was obtained as colorless crystals. Its molecular formula was established as C_{31}H_{38}O_{8} based on the ^{13}C NMR data (Table 2) and high-resolution electrospray ionization mass spectrometry (HRESIMS) at m/z 556.2931 ([M + NH_{4}]^{+}, calcd for 556.2905), indicating 13 indices of hydrogen deficiency. The IR spectrum revealed the presence of hydroxyl (3401 cm^{-1}), carbonyl (1774 cm^{-1}), and olefinic (1641 cm^{-1}) functional groups.
The 1H NMR data of 1 (Table 1) displayed the typical resonances for four singlet methyl groups (δH 0.55, 0.80, 1.69, and 2.02), three oxygenated methine protons (δH 4.31, 4.29, and 4.92), a methoxy group (δH 3.28), and four olefinic protons (δH 5.09, 5.09, 5.26, and 5.28). Its 13C NMR and distortionless enhancement by polarization transfer (DEPT) data (Table 2) showed 31 carbon signals corresponding to an ester carbonyl, six olefinic carbons, six quaternary carbons (four oxygenated), nine methines (two oxymethines), four methyl- enes, a methoxy, and four methyl groups.

Figure 1. Chemical structures of compounds 1–14.

Table 1. 1H NMR (600 MHz) Spectroscopic Data of 1–7 in CDCl3 (δ in ppm, J in Hz)

| position | 1     | 2     | 3     | 4     | 5     | 6     | 7     |
|----------|-------|-------|-------|-------|-------|-------|-------|
| 1        | 1.42 m| 1.40 m| 1.34 m| 1.28 m| 1.27 m| 1.48 m| 1.37 m|
| 2        | 0.86 m, 0.76 m| 0.85 m, 0.76 m| 0.84 m, 0.78 m| 0.85 m, 0.76 m| 0.86 m, 0.70 m| 0.84 m, 0.71 m| 1.02 m, 0.83 m|
| 3        | 2.02 overlapped| 1.98 m| 2.00 m| 2.00 m| 1.96 m| 1.97 overlapped| 2.00 m|
| 5        | 3.33 dt (11.0, 2.5) | 3.34 overlapped| 2.75 brd (11.6) | 3.47 overlapped| 3.38 d (11.2) | 3.57 brd (10.8) | 2.89 brd (12.4) |
| 6        | 4.31 d (11.0) | 4.32 t (11.6) | 4.61 brd (11.6) | 5.55 (10.6) | 5.78 d (11.2) | 5.79 d (10.8) | 5.54 dd (12.4, 1.4) |
| 9        | 2.59 d (14.4) | 2.61 d (14.2) | 2.67 d (13.6) | 2.76 (14.4) | 2.61 d (14.5) | 2.61 d (14.5) | 3.03 d (14.3) | 2.75 d (13.6) |
| 12*      | 4.29 brd (11.5) | 3.84 t (9.8) | 3.81 brd (12.0) | 5.62 d (10.6) | 5.67 d (10.6) | 5.64 d (10.5) | 5.61 d (12.0) |
| 13        | 2.45 d (13.4) | 2.47 d (14.6) | 2.36 d (14.0) | 2.28 d (13.6) | 2.12 d (14.5) | 2.37 d (14.5) | 2.15 d (14.3) | 1.87 d (13.6) |
| 14        | 2.02 d (13.4) | 1.73 d (14.6) | 1.70 d (14.0) | 1.97 d (13.6) | 1.99 d (14.5) | 2.32 d (13.6) | 2.04 d (13.7) |
| 15        | 5.26 brs | 5.25 brs | 5.20 brs | 5.04 brs | 5.02 brs | 5.03 brs | 5.08 brs |
| 12′       | 4.29 s | 4.86 s | 5.09 s | 5.15 s | 5.41 s | 5.98 s | 5.48 s |
| 13′       | 1.69 s | 1.68 s | 1.62 s | 1.86 s | 1.89 s | 1.83 s | 1.84 s |
| 14′       | 0.80 s | 0.83 s | 0.82 s | 0.53 s | 0.56 s | 0.66 s | 0.53 s |
| 15′       | 5.28 brs | 5.07 brs | 5.05 brs | 4.96 brs | 4.99 brs | 4.97 brs | 4.95 brs |
| 5.28 s (8′-OCH3) | 5.09 s | 5.07 s | 5.03 brs | 4.69 brs | 4.72 brs | 4.71 brs | 4.68 brs |
| 3.28 s (8′-OCH3) | 3.77 m, 3.62 m | 3.43 (8′-OCH3) | 3.24 s | 3.06 s | 3.21 s |
| 1.29 t (7.0) | (8′-OCH3) | (8′-OCH3) | 2.12 s (6-OAc) | 2.23 s (6-OAc) | 2.00 s (6-OAc) | 2.20 s (6-OAc) | 2.06 s (6-OAc) | 2.06 s (6-OAc) |
The connections between two sesquiterpenoid units were from H-13 to Cyclic ring for two lindenane sesquiterpenoids (Figure 2). The characteristic exocyclic double bond (H-15) to C-3, C-4, and C-5 was confirmed as shown. The inspection of the 1D and 2D NMR data of I [including 1H−1H COSY, heteronuclear single quantum coherence (HSQC), and heteronuclear multiple bond coherence (HMBC)] suggested that compound I should be a lindenane sesquiterpenoid dimer. The 1H−13C COSY spectrum showed two sets of proton spin systems of a characteristic 1,2-distributed cyclopropane ring for two lindenane sesquiterpenoids (Figure 2). The HMBC correlations from H-13 to C-7, C-11, and C-12, from H-14 to C-1, C-5, C-9, and C-10, and from the protons of the characteristic exocyclic double bond (H-15) to C-3, C-4, and C-5 indicated a sesquiterpenoid unit in I to be strychnistenolide, which was confirmed by comparison with NMR data previously reported in the literature. The remaining NMR data for another sesquiterpenoid unit are similar to those of strychnistenolide, except for an epoxyl group at C-7' and C-11', as indicated by the typical oxygen-bearing carbon resonances at δC 71.6 (C-7') and 66.4 (C-11'), the HMBC from H-13' to C-7', C-11', and C-12', and from H-12' to C-7' and C-11', a methoxyl group at C-8' as suggested by HMBC of −OCH3/C-8', and the absence of the carbonyl group at C-12'. The connections between two sesquiterpenoid units were resolved based on the key HMBC of H-12'/C-8. Hence, the planar structure of I was defined as shown.

The relative configuration of I was assigned by nuclear Overhauser effect spectroscopy (NOECS) correlations, as shown in Figure 2. The NOECS correlations of H-14/H-2, H-14/H-6, H-14'/H-2', and H-14''/H-6' indicated that these protons are cofacial and thus assigned as β-oriented according to those of natural lindenanes. Further examination of the NOECS cross peaks of H-1/H-3/H-5 and H-1''/H-3'/H-5' revealed the α-orientation for these two sets of protons. The key NOECS correlations of H-12'/OCH3-8' and OCH3-8'/H-14' were observed, suggesting that OCH3-8' and H-12' were β-oriented. The resonance of the methyl protons at δH 0.55 due to the anisotropic effect of H-14' was found to be considerably deshielded relative to that of H-14 at δH 0.55 due to the anisotropic effect exhibited by the β−OCH3-8' and α−O-8 groups, consistent with what was observed in previous studies. Recrystallization of I from CHCl3−MeOH afforded single crystals suitable for X-ray diffraction (XRD) with Cu Kα radiation. These XRD results confirmed the assigned planar structure and further supported the assigned absolute configuration (Figure 3).

The configuration of C-8 in natural lindenane-and eudesmane-type sesquiterpene lactones is difficult to be deduced because of the absence of NOE correlations and crystal data. Kouno I. et al. reported the cofacial orientation of C-

### Table 2. 13C NMR (150 MHz) Spectroscopic Data of 1–7 in CDCl3 (δ in ppm)

| position | 1   | 2   | 3   | 4   | 5   | 6   | 7   |
|----------|-----|-----|-----|-----|-----|-----|-----|
| 1        | 29.5| 29.5| 28.0| 29.5| 28.8| 29.4| 28.0|
| 2        | 17.2| 16.9| 16.9| 16.9| 16.9| 17.0| 16.7|
| 3        | 23.7| 24.2| 23.5| 23.8| 23.8| 23.7| 23.7|
| 4        | 149.1| 149.1| 148.2| 148.9| 148.4| 148.9| 147.5|
| 5        | 62.9| 62.5| 70.6| 60.7| 60.4| 60.0| 67.1|
| 6        | 63.2| 63.2| 68.4| 63.4| 63.5| 63.0| 69.6|
| 7        | 157.2| 156.4| 157.2| 153.3| 153.7| 152.7| 155.3|
| 8        | 107.3| 107.7| 108.5| 107.1| 106.2| 107.5| 108.2|
| 9        | 49.9| 49.9| 47.6| 51.2| 50.6| 47.6| 47.3|
| 10       | 38.3| 38.1| 37.9| 37.5| 37.5| 38.0| 38.6|
| 11       | 132.6| 133.0| 128.0| 134.0| 132.8| 132.1| 125.7|
| 12       | 171.1| 170.8| 170.8| 171.2| 171.0| 171.3| 170.5|
| 13       | 9.0 | 8.9 | 9.7 | 9.9 | 9.6 | 9.5 | 8.8 |
| 14       | 22.1| 22.2| 18.6| 21.3| 20.9| 22.0| 18.6|
| 15       | 108.7| 108.7| 109.5| 107.8| 108.0| 107.7| 109.3|
| 1'       | 28.9| 29.9| 30.1| 29.4| 29.2| 29.7| 29.5|
| 2'       | 16.8| 17.1| 17.0| 16.7| 16.5| 16.7| 16.9|
| 3'       | 23.7| 23.8| 23.8| 23.7| 23.5| 23.6| 23.7|
| 4'       | 148.4| 148.9| 149.4| 149.8| 149.2| 149.9| 149.9|
| 5'       | 67.3| 66.5| 65.9| 60.3| 60.9| 60.7| 60.2|
| 6'       | 64.2| 68.4| 69.3| 63.5| 62.8| 63.4| 63.5|
| 7'       | 71.6| 71.1| 71.1| 140.3| 140.8| 140.9| 139.5|
| 8'       | 108.7| 109.5| 107.0| 113.9| 117.4| 115.6| 114.3|
| 9'       | 46.8| 38.5| 39.4| 52.7| 47.9| 52.6| 52.3|
| 10'      | 38.1| 38.9| 38.9| 38.1| 37.9| 37.9| 38.1|
| 11'      | 66.4| 64.3| 63.9| 132.5| 131.3| 133.1| 133.7|
| 12'      | 96.2| 99.2| 101.1| 100.6| 100.7| 104.5| 102.8|
| 13'      | 11.7| 11.0| 12.1| 10.5| 10.6| 10.4| 10.7|
| 14'      | 17.7| 22.1| 21.9| 21.6| 20.7| 21.0| 21.5|
| 15'      | 109.7| 107.3| 107.0| 106.9| 107.2| 104.5| 106.9|
| 8'-OCH3 | 51.6| 57.9, 15.4| 49.4| 6-OAc| 6-OAc| 6-OAc| 6-OAc|
| 8'-OCH3CH3 | 6-OAc| 6-OAc| 6-OAc| 6-OAc| 6-OAc| 6-OAc| 6-OAc|

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8 substituent group can be assigned by the chemical shift of the C-14 methyl protons in lindenane- and eudesmane-type sesquiterpene lactones. In order to confirm the relationship between the proton chemical shift of 14-CH₃ and the configuration of C-8 in natural lindenane- or eudesmane-type sesquiterpene lactones (Table S), we reviewed those data of 31 known and 12 new lindenane- or eudesmane-type sesquiterpene lactones. As shown in Table S, it was observed that the α orientation of 8-R(S) in 22 compounds corresponded with the proton chemical shift of 14-CH₃ in a range of 0.42–0.67 ppm (medium, 0.56 ppm), while a range of 0.82–1.47 ppm (medium, 1.06 ppm) of 14-CH₃ corresponded with the β orientation of 8-S(R). These data supported the approach for discriminating the relative configurations of C8 in lindenane- or eudesmane-type sesquiterpene lactones by their proton chemical shift of 14-CH₃.

Compound 2 was obtained as a white, amorphous powder. Via positive-mode HRESIMS at m/z 570.3086 for [M + NH₄]⁺ (calcld for C₃₂H₄₄NO₈, 570.3061), its molecular formula was determined as C₃₂H₄₀O₈, a molecular weight that exceeded that of compound 1 by a methylene group. Comparison of the ¹H and ¹³C NMR data of 1 and 2 (Tables 1 and 2) indicated that 2 differed from 1 in the presence of an ethoxy group (δH 3.77, 3.62, and 1.26; δC 57.9 and 15.4) instead of an methoxy group in 1. The HMBC between the methylene signals (δH 3.77 and 3.62) and C-8′ indicated that the ethoxy group is at the C-8′ position. The NOESY correlations of 2 suggested the same relative configuration as 1. The ECD spectrum of 2 was consistent with that of 1, indicating that 2 has the same absolute configuration as 1 (Figure S19). Consequently, the structure of linderaggrenolide B (2) was determined as depicted.

Compound 3 shares the same molecular formula (C₃₁H₄₀O₈) as that of 1. The NMR data of 3 (Tables 1 and 2) suggested a 2D structure identical to that of 1. However, the downfield-shifted resonance of H-14 at δH 0.89 was indicative of an 8β oxygen atom (Table S) due to the anisotropic effect. In addition, the downfield shifts of C-12′ (ΔδC 4.90 ppm) and H-12′ (ΔδH 0.17 ppm) suggested that the configuration of C-12′ in 3 was opposite of that of 1. As a consequence, the configuration at C-8 and C-12′ were defined as (8S, 12′R) for 3, which was supported by the opposite cotton effects at 220 nm in ECD spectra of 3 (Figure S29) and 1 (Figure S9). Therefore, the structure of linderaggrenolide C (3) was assigned as shown.

Linderaggrenolide D (4), a white amorphous powder, was assigned a molecular formula of C₃₅H₄₂O₉ as deduced from its

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**Figure 2.** Key ¹H–¹H COSY, HMBC, and NOESY correlations of compounds 1, 8, 10, and 14.

**Figure 3.** ORTEP drawing of compound 1.
sodium adduct ions in the HRESIMS at m/z 629.2720 ([M + Na]⁺, calc for C₃₅H₄₆O₉N, 629.2721). The ¹H and ¹³C NMR spectroscopic data (Tables 1 and 2) suggested that compound 4 shared the same lindenane sesquiterpenoid dimer skeleton as 1.

The main difference between the two compounds was that ⁷',₁₁'-epoxy group in 1 was replaced with a double bond (δC 113.9 and 140.3). This finding was confirmed by HMBC from H-13 to C-⁷' and C-₁₁', and from H-12' to C-⁷' and C-₁₁'. The HMBC from H-6 to δC 171.1 and H-6' to δC 170.5 indicated that two acetoxyl groups were attached to C-6 and C-6', respectively. In addition, the H-14' methyl signal at δC 0.53 of 4 was considerably upfield relative to that of 1 at δC 0.80, supporting the antiparallel relationship of the C-14' methyl group and the ⁸'-OCH₃ group in the case of 4 (Table 5). The NOESY correlation of H-12'/H-14' suggested that H-12' was β-oriented. Furthermore, the absolute configuration of 4 was determined as depicted in Figure 4 by comparison of its experimental and calculated ECD spectra. The calculated ECD spectrum of (1R,3S,5S,6R,8R,10S,1'R,3'S,5'S,6'R,8'R,10'S,12'R)-4 agreed well with the experimental curve (Figure 4). Therefore, the structure of 4 was defined as shown.

Compound 5 was isolated as an amorphous powder with a molecular formula of C₃₄H₄₀O₉ calculated as determined from the ion peak at m/z 610.3040 ([M + NH₄]⁺, calc for C₃₄H₄₀O₉N, 610.3011). The ¹H and ¹³C NMR data of 5 (Tables 1 and 2) were very similar to those of 4, with the only difference being the absence of signals corresponding to ⁸'-OCH₃ and the presence of an additional hydroxyl group. The HMBC from H-6' and H-9' to C-8' and the deshielded signal of C-8' at δC 117.4 confirmed that the ⁸'-OCH₃ group in 4 was replaced by a hydroxyl group in 5. Analysis of the corresponding NOESY spectrum confirmed that the relative configuration of 5 was the same as that of 4. The experimental ECD spectrum of 5 was also consistent with that of 4, suggesting that both features the same absolute configurations (Figure S49). Taken together, the structure of 5 was elucidated as shown and named linderaagnolide E.

Linderaagnolide F (6) and G (7) was found to have the same molecular formula as 4 based on their corresponding HRESIMS data. Analysis of their NMR data (Tables 1 and 2) of 6 and 7 indicated that they have an identical planar structure as 4. The major NMR differences between 6 and 4 were the chemical shifts of C-12' (ΔδC 3.90 ppm) and H-12' (ΔδC 0.83 ppm), suggesting that the configuration of C-12' in 6 was opposite to that of 4. Therefore, the configuration of 12'S was assigned in 6. The ¹H and ¹³C-NMR data of 7 (Tables 1 and 2) were very similar to those of 4 and 6, except for the deshielded H-14 methyl signal at δC 0.95 in 7 (δC 0.56 and 0.59 in 4 and 6, respectively), suggesting that the ₈'-oxygen atom in 7 is β-oriented (Table 5) and the ⁸'S absolute configuration for linderaagnolide G (7).

Linderaagnolide H (8) was isolated as an amorphous powder. Its molecular formula, C₃₀H₃₇ClO₇, was determined by the HRESIMS ion peak in the positive mode at m/z 562.2582 ([M + NH₄]⁺, calc for C₃₀H₃₇ClO₇N, 562.2566). Analysis of the corresponding NMR data (Tables 3 and 4) revealed the presence of two α,β-unsaturated-γ-lactone groups in 8. In addition, six methyls, four methylenes, nine methines (three oxygenated), and eleven quaternary carbons were also distinguished with the aid of DEPT experiments. The aforementioned data suggested that 8 was likely a lindenane-type sesquiterpenoid dimer. However, in-depth NMR data analysis revealed some differences between 8 and the reported common lindenane sesquiterpenoid dimer, lindanolide F. First, the absence of a methylene (δC 2.73, 2.18 and δC 45.2) and the presence of a methyl group (δC 1.11 and δC 33.1) suggested the occurrence of a ring-opening event, and the HMBC of H-9'/
the structure of compound 8–14 in CDCl3 (δ in ppm).

| position | 8  | 9  | 10 | 11 | 12 | 13 | 14 |
|----------|----|----|----|----|----|----|----|
| 1        | 29.4 | 29.4 | 29.4 | 29.4 | 29.4 | 27.8 | 28.2 |
| 2        | 17.0 | 16.9 | 16.9 | 17.0 | 17.0 | 16.8 | 17.3 |
| 3        | 24.0 | 24.0 | 24.0 | 23.8 | 23.8 | 23.7 | 23.7 |
| 4        | 149.4 | 149.0 | 149.2 | 148.6 | 148.5 | 147.0 | 149.1 |
| 5        | 63.2 | 62.9 | 62.9 | 60.3 | 60.3 | 67.8 | 63.5 |
| 6        | 62.9 | 63.5 | 63.5 | 62.9 | 62.9 | 69.7 | 67.2 |
| 7        | 155.4 | 157.3 | 157.3 | 153.3 | 151.4 | 157.3 | 144.9 |
| 8        | 108.4 | 107.8 | 107.7 | 107.0 | 107.9 | 197.9 | 199.5 |
| 9        | 48.2 | 49.7 | 49.8 | 50.7 | 48.4 | 48.1 | 53.2 |
| 10       | 39.1 | 38.0 | 38.0 | 37.5 | 37.9 | 38.3 | 37.1 |
| 11       | 131.4 | 132.9 | 132.8 | 134.1 | 133.8 | 126.0 | 134.9 |
| 12       | 170.8 | 170.7 | 170.8 | 170.5 | 169.8 | 170.4 | 170.6 |
| 13       | 8.9 | 9.1 | 9.1 | 9.9 | 9.7 | 9.1 | 17.8 |
| 14       | 21.8 | 22.1 | 22.1 | 21.4 | 21.7 | 18.2 | 20.0 |
| 15       | 108.2 | 109.3 | 109.2 | 108.1 | 108.1 | 109.5 | 108.7 |
| 1′       | 57.3 | 57.4 | 73.0 | 33.8 | 34.0 | 33.9 | 24.7 |
| 2′       | 46.8 | 46.7 | 56.0 | 10.8 | 11.0 | 11.1 | 15.3 |
| 3′       | 131.0 | 131.4 | 127.9 | 24.7 | 24.6 | 24.6 | 23.6 |
| 4′       | 158.4 | 138.2 | 159.6 | 152.3 | 152.4 | 152.2 | 144.4 |
| 5′       | 63.4 | 63.4 | 62.7 | 51.9 | 51.8 | 51.6 | 132.0 |
| 6′       | 67.1 | 67.0 | 69.0 | 67.8 | 67.6 | 67.6 | 67.6 |
| 7′       | 155.3 | 155.2 | 155.1 | 158.6 | 158.1 | 158.0 | 142.8 |
| 8′       | 98.1 | 95.1 | 95.3 | 94.8 | 97.3 | 95.4 | 167.1 |
| 9′       | 33.1 | 33.0 | 35.5 | 32.7 | 32.6 | 32.6 | 37.0 |
| 10′      | 43.9 | 44.0 | 41.3 | 42.0 | 41.8 | 41.8 | 51.5 |
| 11′      | 131.0 | 130.9 | 131.2 | 128.7 | 128.9 | 129.8 | 141.8 |
| 12′      | 170.7 | 169.3 | 169.3 | 169.2 | 168.9 | 168.4 | 166.4 |
| 13′      | 12.5 | 12.1 | 12.4 | 12.2 | 12.3 | 12.1 | 10.9 |
| 14′      | 19.6 | 19.5 | 20.4 | 23.0 | 23.1 | 23.1 | 24.3 |
| 15′      | 17.4 | 17.4 | 17.1 | 109.9 | 110.0 | 110.1 | 62.9 |

C-1′, C-5′, and C-10′ confirmed that the six-membered ring in lindenane sesquiterpenoid was open at the C-9′ position (Figure 2). Second, the key HMBC of H-8′/C-8 and the deshielded C-8 (δC 108.4) and C-8′ (δC 98.1) suggested that the two sesquisesquiterpenoid units were connected via a bridge of C-8-O–C-8′. Third, the replacement of the chloride group by a methoxyl group in 8′-OAc 6-OAc indicated that the other one cyclopropane ring was open. Considering the presence of a chlorine atom, one deshielded methine group (δH 2.45 and δC 87.9) suggested that the six-membered ring could be replaced by a singlet methyl group (δH 2.45 and δC 87.9). A pair of terminal bond proton signals were replaced by a singlet methyl group (δH 2.45 and δC 87.9). Therefore, the structure of compound 8 could be defined as shown.

Compound 9 was isolated as an amorphous powder. Its molecular formula was determined as C31H40O8, based on its HRESIMS data, which was the same as that of 8. Analysis of the NMR data (Tables 3 and 4) showed that 9 shared the same 2D structure with 8. The major differences between the two compounds were upfield shifts at C-8′ (ΔδC 3.0 ppm) and H-8′ (ΔδH 0.51 ppm) due to different configuration of C-8′. The (1R,3S,5S,6R,8R,10S,1′R,5′S,6′R,8′R) absolute configuration of compound 9 was defined by comparing its experimental and calculated ECD spectra (Figure 4). Therefore, the structure of linderaggrenolide I (9) was assigned as shown.

Table 4. 13C NMR (150 MHz) Spectroscopic Data of 8–14 in CDCl3 (δ in ppm)
Table 5. Relationship between the Proton Chemical Shift of 14-CH₃ and the Configuration of C-8 in Natural Lindene- and Eudesmane-Type Sesquiterpene Lactones

| no. | compounds                      | skeleton | 14-CH₃  (δₚ in ppm) | the orientation of 8-R | the configuration of C-8 | refs |
|-----|--------------------------------|----------|----------------------|------------------------|--------------------------|------|
| 1   | strychnistenolide A            | A        | 0.61 (s)             | OH                     | α                        | R    | 12   |
| 2   | strychnistenolide A acetate    | A        | 0.58 (s)             | OH                     | α                        | R    | 12   |
| 3   | linderolide T                  | A        | 0.55 (s)             | OH                     | α                        | R    | 15   |
| 4   | heterogorgiolide               | A        | 0.52 (s)             | OCH₃                   | α                        | R    | 16   |
| 5   | lindananolide F                | A        | 0.42 (s)             | R                      | α                        | R    | 13   |
| 6   | aggreganoid A                  | A        | 0.48 (s)             | R                      | α                        | S    | 10   |
| 7   | dectone A                      | A        | 0.56 (s)             | R                      | α                        | S    | 17   |
| 8   | 8α-linderalactone              | B        | 0.67 (s)             | OH                     | α                        | R    | 4    |
| 9   | bieptasterolide                | B        | 0.49 (s)             | R                      | α                        | R    | 18   |
| 10  | biactractylenolide II          | B        | 0.51 (s)             | R                      | α                        | R    | 19   |
| 11  | 8α-methoxy-epiasterolid        | B        | 0.65 (s)             | OCH₃                   | α                        | R    | 20   |
| 12  | 1                              | A        | 0.55 (s)             | OR                     | α                        | R    |
| 13  | 2                              | A        | 0.57 (s)             | OR                     | α                        | R    |
| 14  | 4                              | A        | 0.56 (s)             | OR                     | α                        | R    |
| 15  | S                              | A        | 0.58 (s)             | OR                     | α                        | R    |
| 16  | 6                              | A        | 0.59 (s)             | OR                     | α                        | R    |
| 17  | 7                              | A        | 0.66 (s, H-14′)      | OR                     | α                        | R    |
| 18  | 81                            | A        | 0.56 (s)             | OR                     | α                        | R    |
| 19  | 91                            | A        | 0.56 (s)             | OR                     | α                        | R    |
| 20  | 10                            | A        | 0.56 (s)             | OR                     | α                        | R    |
| 21  | 11                            | A        | 0.58 (s)             | OR                     | α                        | R    |
| 22  | 12                            | A        | 0.60 (s)             | OR                     | α                        | R    |
| 23  | strychnistenolide B            | A        | 1.23 (s)             | OH                     | β                        | S    | 12   |
| 24  | strychnistenolide B acetate    | A        | 0.99 (s)             | OH                     | β                        | S    | 12   |
| 25  | 8-O-β-D-glucopyranoside        | A        | 0.93 (s)             | OR                     | β                        | S    | 21   |
| 26  | atractylenolide III            | B        | 1.03 (s)             | OH                     | β                        | S    | 22   |
| 27  | atractylenoide IV              | B        | 1.06 (s)             | OH                     | β                        | S    | 22   |
| 28  | atractylenolther               | B        | 1.05 (s)             | OH                     | β                        | S    | 23   |
| 29  | 4α,8β-dihydroxy-Sr(H) -eudesm-7(11)-en-8,12-olide | B | 1.06 (s) | OH | β | S | 24 |
| 30  | 4α-hydroxy-Sr(H) -8β-methoxy-eudesm-7(11)-en-8,12-olide. | B | 1.06 (s) | OCH₃ | β | S | 24 |
| 31  | atractylenoldone               | B        | 1.06 (s)             | OH                     | β                        | S    | 25   |
| 32  | (3R)-3-hydroxyatractylenoid III | B | 1.32 (s) | OH | β | S | 26 |
| 33  | 8β-hydroxy-1-oxyeudesma-3,7(11)-dien-12,8α-olide | B | 1.20 (s) | OH | β | S | 26 |
| 34  | (3S)-3-hydroxyatractylenoid III 3-O-β-D-Glucopyranoside | B | 1.25 (s) | OH | β | S | 27 |
| 35  | hydroxylindestenolide          | B        | 1.06 (s)             | OH                     | β                        | S    | 28   |
| 36  | linderalactone D               | B        | 1.30 (s)             | OH                     | β                        | S    | 4    |
| 37  | 8β-linderalactone              | B        | 1.06 (s)             | OH                     | β                        | S    | 4    |
| 38  | linderolide I                  | B        | 1.43 (s)             | OH                     | β                        | S    | 29   |
| 39  | linderolide A                  | B        | 1.47 (s)             | OH                     | β                        | S    | 30   |
| 40  | linderolide B                  | B        | 1.44 (s)             | OH                     | β                        | S    | 30   |
| 41  | biatractylenolide              | B        | 1.07 (s)             | R                      | β                        | S    | 31   |
| 42  | bilindestenolide               | B        | 1.21 (s)             | R                      | β                        | S    | 19   |
| 43  | 1                            | A        | 0.80 (s, H-14′)      | OR                     | β                        | S    |
| 44  | 2                            | A        | 0.83 (s, H-14′)      | OR                     | β                        | S    |
| 45  | 3                            | A        | 0.89 (s)             | OR, R                  | β                        | S    |
| 46  | 4                            | A        | 0.82 (s, H-14′)      | OR                     | β                        | S    |

The NOESY correlations of CH₃-9′/H-1′ and H-S′, and H-6′/CH₃-14′ were indicative of 9′-CH₃α, S′-Hα, 1′-Hα, 6′-Hβ, and 14′-CH₃β in 10, equally to those in 9. The resonances for H-8′ and C-8′ agree well with those of 8′R in compound 9, suggesting that 10 exhibits the same configuration as 9. In addition, the highly similar ECD spectra of 9 and 10 also
supported the above notion (Figure S99). Thus, the structure of linderaggrenolide J (10) could be assigned as shown.

Linderaggrenolide K (11) had a molecular formula C_{34}H_{40}O_{9} based on its HRESIMS (m/z 610.3021 [M + NH\textsubscript{4}]\textsuperscript{+}). The NMR data of 11 (Tables 3 and 4) suggested that compound 11 is structurally closely related to 10. The only differences were the absence of the methoxyl group, the presence of a 1,2-distributed cyclopropane, and the migration of the C3′=C4′ double bond to C4′=C15′. These changes were confirmed by the HMBC of H-15′/C-3′, C-4′, and C-5′, and 1H−1H COSY correlations of H-1′/H-2′/H-3′. In addition, the HMBC of H-6 and H-6′ with acetyl carbonyl (δ\textsubscript{C} 171.3 and δ\textsubscript{C} 169.5) indicated that the additional two acetoxyl groups were attached to C-6 and C-6′, respectively. Analysis of NOESY correlations indicated that 11 adopted the same relative configuration as 10. The absolute configuration of 11 was defined as (1R,3S,5S,6R,8R,10S,1′R,3′S,5′R,6′R,8′R)-11 by comparison of its experimental and calculated ECD spectra (Figure 4).

The same molecular formula, C_{31}H_{34}O_{8}, for both compounds 12 and 13 was established based on the corresponding HRESIMS data at m/z 610.3027 [M + NH\textsubscript{4}]\textsuperscript{+} and 610.3014 [M + NH\textsubscript{4}]\textsuperscript{+}, respectively. Analysis of the NMR data (Tables 3 and 4) suggested that both 12 and 13 shared the same planar structure as 11, except for the configurations of C-8 and C-8′. The chemical shifts of H-8′ (δ\textsubscript{H} 5.78) and C-8′ (δ\textsubscript{C} 97.3) of 12 were deshielded in comparison to those of 11 (δ\textsubscript{C} 94.8 and δ\textsubscript{H} 5.44), suggesting that the configuration of C-8′ in 12 was opposite to that of 11. Meanwhile, the H-14 methyl signal of 13 at δ\textsubscript{H} 0.83 was found to be deshielded relative to that of 11 at δ\textsubscript{H} 0.58 due to the anisotropic effect of the 8β oxygen atom, suggesting that the configuration of C-8 in 13 was opposite to that of 11. The ECD spectra of 12 and 8 were very similar, suggesting the (8′S) absolute configuration of 12 as shown. It is worth mentioning that the configuration of C-8′ has a profound influence on the ECD curve, while the configuration of C-8 does not. Therefore, the structures for linderaggrenolide L (12) and linderaggrenolide N (13) were proposed as shown.

Compound 14 was assigned the molecular formula of C_{31}H_{36}O_{8} on the basis of the quasimolecular ion peak at m/z 557.2151 [M + Na]\textsuperscript{+} in the positive-mode HRESIMS spectrum. The 13C NMR and DEPT data (Tables 3 and 4) showed 31 signals corresponding to five methyl, six methylene, seven methine, and thirteen quaternary carbons. The 1H−1H COSY spectrum showed the presence of two cyclopropane rings. Furthermore, compound 14 contained an acetyl group due to the presence of resonance signals at δ\textsubscript{C} 170.4, 21.1 and δ\textsubscript{H} 2.07. The presence of two lindenane sesquiterpenoid (units A and B) in 14 was elucidated by comprehensive analysis of the 2D NMR spectra. In unit A, the HMBC from H-6 to H-9 to C-8 suggested that the C-8 position of unit A was a carbonyl carbon (Figure 2). Moreover, the HMBC cross peaks of H-13/C-7, C-3, and C-12 confirmed the furan lactone ring in unit A was open. The NMR data of unit B were very similar to those of lindenanolide E. The one significant difference was the absence of an aldehyde group. NOESEY correlations were observed among the following proton signals: H-2′ to H-1/H-14, which confirmed that unit B had the same relative configuration as lindenanolide E. Finally, the two units were proposed to be linked via an oxygen atom between C-12 and C-15′ based on the HMBC networks of H-15′/C-12, C-3′, C-4′, and C-5′. Thus, the structure of linderaggrenolide N (14) was identified as shown.

Although sesquiterpenoids were reported as the characteristic constituents of L. aggregata, sesquiterpenoid dimers were rarely found in this plant. To date, most sesquiterpenoid dimers have been reported from the Chloranthaceae family. The disesquiterpenoids found in this study may represent a group of metabolites with taxonomic significance for L. aggregata.
From a structural perspective, linderaggrenolides A−N (1−14), belonging to the pseudo-disesquiterpenoid family, could be easily distinguished since two sesquiterpenoids were found to be connected via an oxygen bridge. According to the results reported previously, lindenane sesquiterpenoid dimers are mainly formed by Diels−Alder or hetero-Diels−Alder reactions, and the two units are generally linked directly by one or two C−C bonds. However, lindenane sesquiterpenoid dimers containing an oxygen bridge have been rarely reported from nature. Therefore, the linkage feature of these compounds also underscores the chemical diversity of sesquiterpenoid dimers. Therefore, it is likely that both compounds 8 and 9 are natural chlorine-containing substances.

All isolated compounds were tested for their TGF-β inhibitory activity. As shown in Figure 5, compounds 8 and 9 significantly downregulated the p-smad2 expression in a concentration-dependent manner without any impact on the expression of smad2 and β-actin protein, with the IC_{50} values of 25.91 and 21.52 μM, respectively. These data suggested that the chlorines in these compounds should be important for their TGF-β inhibitory activity.

3. EXPERIMENTAL SECTION

3.1. General Experimental Procedures. Melting point was obtained on a BA-350 (BenAng) melting point apparatus. Optical rotations were measured on a Rudolph Research Autopol I automatic polarimeter. UV and ECD spectra were recorded on a JASCO High Performance J-1500 CD spectrometer. NMR spectra were obtained at 600 MHz for 1H NMR and 150 MHz for 13C NMR, respectively, using a Bruker Ascend 600 spectrometer. HRESIMS data were acquired on an Agilent Technologies 6230 Accurate Mass Q-TOF UHPLC/MS spectrometer.

3.2. Plant Material. The dried roots of L. aggregata were collected from the Zhejiang Province, China, in March 2017, and identified by Dr. G. Y. Zhu. The voucher specimen (LA-201703) was deposited at the State Key Laboratory of Quality Research in Chinese Medicines, Macau University of Science and Technology.

3.3. Extraction and Isolation. The dried roots of L. aggregata were ground to powder and extracted with 80% EtOH (4 × 12 L) under reflux. The extract was then concentrated in vacuo at 50 °C. The extract was successively partitioned with petroleum ether (60−90 °C), EtOAc, and n-butanol. After solvent removal, the petroleum ether fraction (145.0 g) was subjected to silica gel column chromatography (CC), eluted with a gradient of increasing EtOAc (0−100%) in petroleum ether to afford six fractions (Fr. 1−Fr. 6) and judged by TLC analysis. Fr. 2 (20.5 g) was subjected to CC on RP C-18 gel and eluted with MeCN−H2O (40:60 to 100:0) to provide seven subfractions (Fr. 2-1−Fr. 2-7). Fr. 2-5 and Fr. 2-6 were initially subjected to RP-C8 column chromatography and eluted with MeCN−H2O and further purified by semipreparative HPLC eluted with MeOH−H2O to obtain compounds 4 (3.5 mg), 5 (6.0 mg), 6 (2.5 mg), 7 (2.0 mg), 11 (8.0 mg), 12 (10.0 mg), 13 (2.5 mg), and 14 (2.0 mg). Fr. 3 (15.0 g) was separated in fashions similar to Fr. 2 to obtain compounds 1 (10.0 mg), 2 (3.0 mg), 3 (5.0 mg), 8 (3.0 mg), 9 (6.5 mg), and 10 (2.0 mg).

3.3.1. Linderaggrenolide A (1). Colorless crystal; m.p. 237−238 °C; [α]_{D}^{25.3} = −21.2 (c 0.3, MeOH); UV (MeOH) \( \lambda_{\text{max}}(\log e) \): 196 (4.32), 230 (4.10), 300 (3.46); ECD (MeOH): 200 (\( \Delta \varepsilon = +4.14 \)), 220 (\( \Delta \varepsilon = −5.12 \)), 254 (\( \Delta \varepsilon = +0.79 \)), 295 (\( \Delta \varepsilon = −0.50 \)) nm; IR, \( \nu_{\text{max}} \): 3401, 2960, 2362, 1774, 1641, 1538, 1462, 1362, 1240, 1094, 671 cm\(^{-1}\); H and 13C NMR (CDCl\(_3\)), see Tables 1 and 2; HRESIMS m/z 556.2931: [M + NH\(_4\)]\(^{+}\) (calcd for C_{33}H_{40}O_{8}N_{4}H\(_4\) 556.2905).

3.3.2. Linderaggrenolide B (2). White powder, [α]_{D}^{25.3} = −2.6 (c 0.3, MeOH); UV (MeOH) \( \lambda_{\text{max}}(\log e) \): 196 (4.34), 230 (3.92), 300 (2.88); ECD (MeOH): 200 (\( \Delta \varepsilon = +24.26 \)), 220 (\( \Delta \varepsilon = −15.23 \)), 254 (\( \Delta \varepsilon = +0.56 \)) nm; IR, \( \nu_{\text{max}} \): 3454, 2929, 2362, 1773, 1656, 1387, 1072, 1007, 920, 740 cm\(^{-1}\); H and 13C NMR (CDCl\(_3\)), see Tables 1 and 2; HRESIMS m/z 570.3086: [M + NH\(_4\)]\(^{+}\) (calcd for C_{35}H_{48}O_{8}N_{4}H\(_4\) 570.3061).

Figure 5. Compounds 8 and 9 blocked TGF-β, inducing smad2 phosphorylation in a dose-dependent manner.
3.3.3. Linderaggrenolid C (3). White powder, [α]D 23.5 +100.0 (c 0.3, MeOH); UV (MeOH) λmax (log ε) 196 (4.44), 225 (4.11), 290 (3.07); ECD (MeOH): 205 (Δε +19.56), 248 (Δε +4.92) nm; IR, νmax: 3441, 2928, 2361, 1770, 1385, 1082, 980, 737 cm⁻¹; 1H and 13C NMR (CDCl₃), see Tables 1 and 2; HRESIMS m/z 556.2917: [M + NH₄]⁺ (calcd for C₃₁H₃₈O₈N₂H₄, 556.2905).

3.3.4. Linderaggrenolid D (4). White powder, [α]D 23.5 +28.8 (c 0.3, MeOH); UV (MeOH) λmax (log ε) 196 (4.28), 225 (3.75); ECD (MeOH): 200 (Δε +14.62), 220 (Δε −7.44), 237 (Δε +1.64), 260 (Δε −1.31) nm; IR, νmax: 3365, 2964, 2362, 1771, 1645, 676 cm⁻¹; 1H and 13C NMR (CDCl₃), see Tables 1 and 2; HRESIMS m/z 629.2720: [M + Na]⁺ (calcd for C₃₃H₄₀O₈Na, 629.2721).

3.3.5. Linderaggrenolid E (5). White powder, [α]D 23.5 −3.1 (c 0.3, MeOH); λmax (log ε) 196 (4.48), 230 (4.00); ECD (MeOH): 200 (Δε +14.62), 220 (Δε −7.44), 237 (Δε +1.64), 260 (Δε −1.31) nm; IR, νmax: 3449, 2361, 1738, 1519, 1373, 1291, 1024, 675 cm⁻¹; 1H and 13C NMR (CDCl₃), see Tables 1 and 2; HRESIMS m/z 610.3040: [M + NH₄]⁺ (calcd for C₃₉H₄₃O₈N₂H₄, 610.3011).

3.3.6. Linderaggrenolid F (6). White powder, [α]D 23.5 +4.6 (c 0.3, MeOH); λmax (log ε) 196 (4.39), 230 (3.86); ECD (MeOH): 200 (Δε +11.43), 218 (Δε −3.87) nm; IR, νmax: 3365, 2362, 1771, 1645, 1387 cm⁻¹; 1H and 13C NMR (CDCl₃), see Tables 1 and 2; HRESIMS m/z 629.2725: [M + Na]⁺ (calcd for C₃₃H₄₀O₈Na, 629.2721).
proceed on ice for 30 min. Protein samples were subjected to electrophoresis in 10% SDS–PAGE gel and transferred onto nitrocellulose membrane (NC membrane). The membranes were blocked in 5% BSA and incubated at 4 °C with primary antibody overnight, followed by a secondary antibody for 1 h at room temperature. Protein bands were detected using a LI-COR Odyssey imaging system (Lincoln, NE, USA). Epigallocatechin gallate (EGCG) was used as the positive control.

Primary antibodies against p-smad2 and smad2 were purchased from Cell Signaling Technology (Beverly, MA, USA). The primary antibody against β-actin was purchased from Abcam Inc. (Cambridge, MA, USA). Secondary antibodies, goat antimouse/antirabbit IgG H&L (IRDye 800CW), were purchased from Abcam Inc. (Cambridge, MA, USA).

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.0c06349.

HRESIMS, IR, UV, CD, 1H and 13C NMR, DEPT, HSQC, HMBC, COSY, and NOESY spectra of compounds 1–14 (PDF)

Single-crystal X-ray diffraction data for compound 1 (CIF).

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Notes
The authors declare no competing financial interest.

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