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Acid-catalyzed transformation of cassane diterpenoids from *Caesalpinia bonduc* to aromatic derivatives†

 Ting Liu,^{ab} Zunxi Ning,^{ab} Yan Yin,^{ab} Shizhou Qi^{ab} and Huiyuan Gao^{ID}*^{ab}

Transformations of cassane diterpenoids from *Caesalpinia bonduc* into aromatic derivatives, either in CDCl₃ or in CHCl₃ irradiated with UV light or catalyzed by AlCl₃, were described. Caesalmin C (**2**) was hydrolyzed with Na₂CO₃ upon refluxing in MeOH to yield compound **1**. Dissolving compound **1** with CDCl₃ resulted in an unexpected aromatization process of a C ring to obtain **1a**, and aromatic derivatives 6-acetoxy-3-deacetycaesaldehydine (**2a**), caesalmin A (**3a**), caesaldehydine (**5a**), caesalmin MC (**5b**), 2-acetycaesaldehydine (**6a**) and new compound **6b** could be obtained from corresponding cassane diterpenoids (**2–8**) under the same conditions. Furthermore, the photochemical reactions of cassane diterpenoids **1–8** occurring in CHCl₃ also yielded aromatic derivatives **1a**, **2a**, **3a**, **5a**, **6a**, new compounds **2b** and **3b**, and 17-norcassane diterpenoids norcaesalmin MC (**2c**) and caesalmin J (**3c**). In addition, cassane diterpenoids **1–8**, treated with AlCl₃ in CHCl₃ or CH₂Cl₂, gave the same results in CDCl₃ and with even shorter reaction time. The role of AlCl₃ in the aromatization of **1** has been explained by DFT calculations.

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1 Introduction

Cassane diterpenoids, a group of rearranged abietane metabolites, have been isolated from different species of medicinal plants of the *Caesalpinia* genus in recent years, and have received much attention for their wide range of pharmacological activities including anti-inflammatory, antitumor, antimalarial, antimicrobial, antiviral, antioxidant and antinociceptive properties.¹ Among these compounds with great structural diversity, some of these bearing an aromatic C ring have earned special attention due to their significant biological activities. Researchers have synthesized some of these interesting diterpenoids including benthamin **1**,² taepenin D,³ taepenin F,⁴ (5 α)-vouacapane-8(14),9(11)-diene,⁵ sucutinirane C and sucutiniran D⁶ from commercially available materials. In this paper the transformation of cassane-type diterpenoids with a fused furan ring into aromatic derivatives in CDCl₃, or upon irradiation with UV light in CHCl₃, or catalyzed by AlCl₃ in CHCl₃ or CH₂Cl₂ at room temperature, was described.

2 Experimental

2.1 General experimental procedures

Optical rotation was measured in MeOH solution on an Anton-Paar MCP 200 polarimeter at room temperature. NMR spectra were recorded on Bruker ARX-400 and AV-600 instruments (Bruker Corporation, Bremen, Germany) with tetramethylsilane as the internal standard. HRESIMS spectra were recorded on a Bruker micro-TOF-Q mass spectrometer. Silica gel (100–200 mesh, and 200–300 mesh) for open-column chromatography and TLC plates (GF₂₅₄) was purchased from Qingdao Marine Chemical Co. Ltd. (Qingdao, China). The HPLC system consisted of a Shimadzu LC-20AR instrument equipped with a SPD-20A UV detector (Shimadzu, Kyoto, Japan) and a YMC C-18 reversed-phase column (5 μ m, 20 \times 250 mm) (YMC, Kyoto, Japan).

2.2 Plant material

The seeds of *Caesalpinia bonduc* (L.) Roxb. (a synonym for *Guilandina bonduc* L.) were purchased from An Guo Medicinal Material Corporation (Hebei Province, China), and authenticated by Associated Prof. Jiuzhi Yuan, Shenyang Pharmaceutical University, Shenyang, China. A voucher specimen (No. SY-2018-01A) was deposited in the Department of Natural Products Chemistry, Shenyang Pharmaceutical University, Shenyang, China.

2.3 Extraction and isolation

The powdered air-dried seed kernels (12.0 kg) of *C. bonduc* were defatted three times with petroleum ether, and then were

^aSchool of Traditional Chinese Materia Medica, Shenyang Pharmaceutical University, Shenyang 110016, People's Republic of China. E-mail: sypugaohy@163.com; Tel: +86-024-43520781

^bKey Laboratory of Structure-Based Drug Design & Discovery of Ministry of Education, Shenyang Pharmaceutical University, Shenyang 110016, People's Republic of China

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extracted with 75% ethanol for three times. The mixture was filtered and the filtrate concentrated *in vacuo* in a rotary evaporator. The concentrated extract was suspended in water and partitioned with CHCl_3 and *n*-BuOH, successively. The residue of the CHCl_3 (214.0 g) was subjected to silica gel column chromatography eluted with CH_2Cl_2 -MeOH (100 : 0 to 1 : 1) to yield ten constituents (constituents 1–10). Constituent 2 (18.8 g) (CH_2Cl_2 -MeOH = 50 : 1) was isolated by silica gel column chromatography using gradient solvent system of petroleum ether-EtOAc (15 : 1 to 2 : 1) to give five constituents (constituents 2.1–2.5). Constituent 2.2 (petroleum ether-EtOAc = 10 : 1) was subjected to preparative RP-HPLC with MeOH-H₂O (65 : 35) to afford compounds 2 (600.0 mg), 6 (125.5 mg) and 9 (45.5 mg). Constituent 2.3 (petroleum ether-EtOAc = 5 : 1) was applied to RP-HPLC with MeOH-H₂O (65 : 35) to get compounds 5 (35.2 mg) and 11 (29.5 mg), and further purified using preparative TLC plate with CH_2Cl_2 -acetone (25 : 1) to obtain compound 10 (38.5 mg). Constituent 2.4 (petroleum ether-EtOAc = 3 : 1) was purified by RP-HPLC with MeOH-H₂O (55 : 45) to yield compounds 7 (30.2 mg) and 8 (93.0 mg). Constituent 3 (38.3 g) (CH_2Cl_2 -MeOH = 25 : 1) was subjected to silica gel column chromatography eluted with petroleum ether-EtOAc gradient (10 : 1–1 : 1) to give five constituents (constituents 3.1–3.5). Constituent 3.1 (petroleum ether-EtOAc = 10 : 1) was further applied to silica gel column with petroleum ether-EtOAc (7 : 1–1 : 1) and isolated by RP-HPLC with MeOH-H₂O (65 : 35) to furnish compounds 3 (85.5 mg) and 4 (65.0 mg).

2.4 Deacetylation of caesalmin C (2)

To a solution of compound 2 (25.0 mg, 0.053 mmol) in methanol (10 mL) was added Na_2CO_3 (28 mg, 0.264 mmol). After refluxing for 1 h, the solvent was removed under reduced pressure and CH_2Cl_2 (20 mL) was added. The organic extract was washed successively with 2 M HCl (5 mL \times 2) and saturated NaCl (5 mL \times 2) and dried with anhydrous Na_2SO_4 . The solution was filtrated and the solvent was removed under reduced pressure, and 18.0 mg (72%) of compound 1 was obtained as a white amorphous powder.

2.5 Aromatization of compound 1 in CDCl_3

Compound 1 (1.0 mg) was dissolved in deuterated chloroform (CDCl_3 , 0.6 mL) at room temperature, and the solution instantly turned pink and quickly became canary yellow, resulting in the formation of compound 1a as evidenced by TLC, which showed a blue spot after being visualized with vanillin-sulfuric acid while compound 1 dissolved in methanol showed an aubergine spot with different R_f values under the same separating condition. Vaporizing CDCl_3 and compound 1a was obtained.

2.6 Aromatization of compounds 2–11 in CDCl_3

Compounds 2–11 (0.0025 mmol) were dissolved in CDCl_3 (0.6 mL) at room temperature, and the formation of aromatic derivatives was monitored by TLC. When the reactant disappeared, the reaction was quenched by evaporating the CDCl_3 , and the residue was purified by HPLC (C18 column) eluted with

MeOH-H₂O (65 : 35) or silica gel column chromatography eluted with petroleum ether-EtOAc.

2.7 Photochemical reaction of compounds 1–11 in CHCl_3

A solution of cassane diterpenoid (0.01 mmol) in CHCl_3 (5.0 mL) was irradiated with a UV lamp (254 nm) at room temperature. After the starting material was consumed, the solvent was removed under reduced pressure and the residue was subjected to HPLC (C18 column) eluted with MeOH-H₂O (65 : 35) or silica gel column chromatography eluted with petroleum ether-EtOAc.

2.8 Aromatization of compounds 1–11 catalyzed by AlCl_3

AlCl_3 (0.012 mmol) was added to a solution of reactant (0.012 mmol) in CHCl_3 (5 mL) and stirred at room temperature until the reactant couldn't be detected by TLC. The mixture was filtrated and then washed with water (2 mL \times 3) and dried with anhydrous Na_2SO_4 . The solvent of the organic layer was evaporated under reduced pressure, and aromatic derivative was obtained by silica gel column chromatography eluted with petroleum ether-EtOAc.

2.8.1 1 α ,5 α ,6 α ,7 β -Tetrahydrovoucapane-14(17)-ene (1). White amorphous powder; ¹H NMR (600 MHz, CD_3OD) δ 7.27 (1H, d, J = 2.0 Hz, H-16), 6.48 (1H, d, J = 2.0 Hz, H-15), 5.38 (1H, br s, H-17), 5.20 (1H, br s, H-17), 4.02 (1H, dd, J = 9.4, 8.6 Hz, H-7), 3.80 (1H, d, J = 8.6 Hz, H-6), 3.70 (1H, br s, H-1), 2.84 (1H, td, J = 11.4, 5.3 Hz, H-9), 2.74 (1H, dd, J = 16.1, 5.3 Hz, H-11), 2.52 (1H, dd, J = 16.1, 11.4 Hz, H-11), 2.29 (1H, ddt, J = 11.4, 9.4, 2.2 Hz, H-8), 2.03 (1H, m, H-2), 1.97 (1H, m, H-3), 1.61 (1H, m, H-2), 1.29 (3H, s, H₃-19), 1.26 (3H, s, H₃-18), 1.10 (3H, s, H₃-20), 1.01 (1H, m, H-3); ¹³C NMR (150 MHz, CD_3OD) δ 153.0 (C, C-12), 142.7 (CH, C-16), 142.1 (C, C-14), 120.9 (C, C-13), 107.5 (CH, C-15), 106.7 (CH₂, C-17), 81.2 (C, C-5), 77.4 (CH, C-1), 75.6 (CH, C-6), 73.6 (CH, C-7), 45.1 (C, C-10), 44.3 (CH, C-8), 39.9 (C, C-4), 39.3 (CH, C-9), 33.3 (CH₂, C-3), 32.1 (CH₃, C-18), 26.4 (CH₂, C-11), 25.8 (CH₃, C-19), 23.9 (CH₂, C-2), 17.2 (CH₃, C-20); HRESIMS m/z 371.1829 [M + Na]⁺ (calcd for $\text{C}_{20}\text{H}_{28}\text{O}_5\text{Na}$, 371.1834).

2.8.2 1 α ,5 α ,6 α -Trihydroxy-14-methylvoucapane-8(14),9(11)-diene (1a). White amorphous powder; $[\alpha]_D^{20}$ +25 (c 0.25, MeOH); ECD (MeOH) λ_{max} ($\Delta\epsilon$) 214 (+13.32), 254 (−1.55), 276 (+2.02) nm; ¹H NMR (600 MHz, CDCl_3) δ 7.55 (1H, d, J = 2.3 Hz, H-16), 7.42 (1H, s, H-11), 6.75 (1H, d, J = 2.3 Hz, H-15), 4.56 (1H, m, H-1), 4.52 (1H, t, J = 7.8 Hz, H-6), 3.28 (1H, dd, J = 16.9, 7.4 Hz, H-7), 2.81 (1H, dd, J = 16.9, 8.1 Hz, H-7), 2.41 (3H, s, H₃-17), 2.18 (1H, m, H-2), 2.14 (1H, m, H-3), 1.94 (1H, m, H-2), 1.34 (3H, s, H₃-18), 1.33 (3H, s, H₃-19), 1.27 (3H, s, H₃-20), 1.18 (1H, m, H-3); ¹³C NMR (150 MHz, CDCl_3) δ 154.0 (C, C-12), 144.7 (CH, C-16), 140.0 (C, C-9), 128.8 (C, C-14), 128.1 (C, C-8), 126.1 (C, C-13), 105.2, (CH, C-15), 104.6 (CH, C-11), 78.5 (C, C-5), 73.6 (CH, C-1), 69.7 (CH, C-6), 49.1 (C, C-10), 38.9 (C, C-4), 36.4 (CH₂, C-7), 32.4 (CH₂, C-3), 30.9 (CH₃, C-18), 28.8 (CH₃, C-20), 25.2 (CH₃, C-19), 25.1 (CH₂, C-2), 16.1 (CH₃, C-17); HRESIMS m/z 353.1723 [M + Na]⁺ (calcd for $\text{C}_{20}\text{H}_{26}\text{O}_4\text{Na}$, 353.1729).



2.8.3 5 α -Hydroxy-1 α ,6 α ,7 β -trihydroxy-14-methylvoucapane-8(14),9(11)-diene (2b). White amorphous powder; ^1H NMR (600 MHz, CD_3OD) δ 7.70 (1H, d, $J = 2.2$ Hz, H-16), 7.04 (1H, s, H-11), 6.88 (1H, d, $J = 2.2$ Hz, H-15), 6.43 (1H, d, $J = 5.3$ Hz, H-7), 5.96 (1H, d, $J = 5.3$ Hz, H-6), 5.68 (1H, t, $J = 3.8$ Hz, H-1), 2.31 (3H, s, H₃-17), 2.21 (1H, m, H-2), 2.13 (3H, s, 6-OCOCH₃), 2.02 (3H, s, 7-OCOCH₃), 1.97 (1H, m, H-3), 1.90 (3H, s, 1-OCOCH₃), 1.89 (1H, m, H-2), 1.59 (3H, s, H₃-20), 1.24 (3H, s, H₃-18), 1.22 (3H, s, H₃-19), 1.19 (1H, m, H-3); ^{13}C NMR (150 MHz, CD_3OD) δ 172.8 (C, 6-OCOCH₃), 172.5 (C, 7-OCOCH₃), 171.2 (C, 1-OCOCH₃), 155.9 (C, C-12), 146.7 (CH, C-16), 141.6 (C, C-9), 131.8 (C, C-14), 128.0 (C, C-13), 127.7 (C, C-8), 106.5 (CH, C-15), 105.1 (CH, C-11), 80.9 (C, C-5), 78.3 (CH, C-6), 76.8 (CH, C-1), 76.7 (CH, C-7), 50.1 (C, C-10), 39.7 (C, C-4), 33.6 (CH₂, C-3), 30.8 (CH₃, C-18), 29.3 (CH₃, C-20), 25.2 (CH₃, C-19), 23.4 (CH₂, C-2), 22.0 (CH₃, 6-OCOCH₃), 21.1 (CH₃, 7-OCOCH₃), 21.0 (CH₃, 1-OCOCH₃), 16.1 (CH₃, C-17); HRESIMS m/z 495.1989 [M + Na]⁺ (calcd for C₂₆H₃₂O₈Na, 495.1995).

2.8.4 1 α -Acetoxy-5 α ,6 α -dihydroxy-7 β -methoxy-14-methylvoucapane-8(14),9(11)-diene (3b). White amorphous powder; $[\alpha]_{\text{D}}^{20} +8$ (c 0.22, MeOH); ECD (MeOH) λ_{max} ($\Delta\epsilon$) 212 (−15.27), 252 (7.38) nm; ^1H NMR (600 MHz, CD_3OD) δ 7.66 (1H, d, $J = 2.2$ Hz, H-16), 6.93 (1H, s, H-11), 6.87 (1H, d, $J = 2.2$ Hz, H-15), 5.59 (1H, t, $J = 3.7$ Hz, H-1), 4.67 (1H, d, $J = 4.3$ Hz, H-7), 4.51 (1H, d, $J = 4.3$ Hz, H-6), 3.62 (3H, s, 7-OCH₃), 2.49 (3H, s, H₃-17), 2.19 (1H, m, H-2), 1.97 (1H, m, H-3), 1.90 (3H, s, 1-OCOCH₃), 1.86 (1H, m, H-2), 1.48 (3H, s, H₃-20), 1.39 (3H, s, H₃-19), 1.36 (3H, s, H₃-18), 1.15 (1H, m, H-3); ^{13}C NMR (150 MHz, CD_3OD) δ 171.5 (C, 1-OCOCH₃), 155.8 (C, C-12), 146.2 (CH, C-16), 141.5 (C, C-9), 132.5 (C, C-14), 130.5 (C, C-8), 127.7 (C, C-13), 106.2 (CH, C-15), 104.6 (CH, C-11), 86.1 (CH, C-7), 81.0 (C, C-5), 77.3 (CH, C-1), 76.9 (CH, C-6), 57.5 (CH₃, 7-OCH₃), 49.1 (C, C-10), 40.0 (C, C-4), 33.9 (CH₂, C-3), 31.3 (CH₃, C-18), 29.0 (CH₃, C-20), 25.9 (CH₃, C-19), 23.6 (CH₂, C-2), 21.1, (CH₃, 1-OCOCH₃), 16.2 (CH₃, C-17); HRESIMS m/z 425.1935 [M + Na]⁺ (calcd for C₂₃H₃₀O₆Na, 425.1940).

2.8.5 1 α ,2 α ,3 α -Triacetoxy-5 α -hydroxy-15,16-dihydro-14-methylvoucapane-8(14),9(11)-diene (6b). White amorphous powder; $[\alpha]_{\text{D}}^{20} -48$ (c 0.23, MeOH); ECD (MeOH) λ_{max} ($\Delta\epsilon$) 220 (−17.99), 240 (2.37) nm; ^1H NMR (600 MHz, CD_3OD) δ 6.24 (1H, s, H-11), 5.90 (1H, d, $J = 3.2$ Hz, H-1), 5.69 (1H, t, $J = 3.6$ Hz, H-2), 5.23 (1H, d, $J = 3.8$ Hz, H-3), 4.47 (1H, dt, $J = 16.9$, 8.6 Hz, H-16), 4.45 (1H, dt, $J = 16.9$, 8.6 Hz, H-16), 3.10 (2H, t, $J = 8.6$ Hz, H₂-15), 2.75 (1H, m, H-7), 2.67 (1H, m, H-7), 2.13 (3H, s, H₃-17), 2.11 (3H, s, 3-OCOCH₃), 2.09 (1H, m, H-6), 2.01 (1H, m, H-6), 1.97 (3H, s, 2-OCOCH₃), 1.96 (3H, s, 1-OCOCH₃), 1.44 (3H, s, H₃-20), 1.29 (3H, s, H₃-19), 1.18 (3H, s, H₃-18); ^{13}C NMR (150 MHz, CD_3OD) δ 171.7 (C, 3-OCOCH₃), 171.5 (C, 2-OCOCH₃), 171.3 (C, 1-OCOCH₃), 159.2 (C, C-12), 143.5 (C, C-9), 133.9 (C, C-14), 126.6 (C, C-8), 125.2 (C, C-13), 102.8 (CH, C-11), 78.2 (CH, C-3), 77.3 (C, C-5), 74.9 (CH, C-1), 71.8 (CH₂, C-16), 68.0 (CH, C-2), 49.3 (C, C-10), 44.0 (C, C-4), 31.1 (CH₃, C-20), 29.9 (CH₂, C-15), 25.4 (CH₃, C-19), 25.3 (CH₂, C-6), 24.2 (CH₂, C-7), 23.5 (CH₃, C-18), 21.0, (CH₃, 1-OCOCH₃), 20.9, (CH₃, 3-OCOCH₃), 20.6, (CH₃, 2-OCOCH₃), 16.3 (CH₃, C-17); HRESIMS m/z 497.2146 [M + Na]⁺ (calcd for C₂₆H₃₄O₈Na, 497.2151).

2.9 Computational methods

The B3LYP density functional method was employed in this work to carry out all the computations. Empirical dispersion GD3BJ was also considered. The 6-31G (d,p) basis set was used for the atoms in geometry optimizations. Vibrational frequency analyses at the same level of theory were performed on all optimized structures to characterize stationary points as local minima or transition states. Furthermore, intrinsic reaction coordinate (IRC) computations were carried out to confirm that transition states connect to the appropriate reactants and products. The Gaussian 09 program package was used throughout.

3 Results and discussion

The fast facile aromatization process in CDCl_3 occurred when we attempted to obtain the NMR spectra of hydrolysate of caesalmin C (2),⁷ a cassane-type diterpenoid isolated from both *Caesalpinia Minax* Hance and *Caesalpinia bonduc* (L.) Roxb. in our previous work. Compared with other cassane diterpenoids isolated from seeds of above two plants of *Caesalpinia* genus, caesalmin C (2) has relatively high abundance but no distinct bioactivity in our previous activity screening. For this reason, caesalmin C (2) was deacetylated with Na_2CO_3 by refluxing in MeOH for 1 h. Upon completion of the deacetylation, product 1 dissolved in CDCl_3 could quickly transformed to aromatic derivative 1a, as evidenced by thin layer chromatography (TLC) behavior and NMR data. Aromatization reactions of caesalmin C (2),⁷ bonducellpin G (4),⁸ caesalmin E (7)⁷ and caesalmin F (8)⁷ to 6-acetoxy-3-deacetoxycaesaldehydine (2a),⁹ ζ -caesalpin (3)¹⁰ to caesal A (3a),¹¹ caesalpinin C (5)¹² to caesaldehydine (5a),¹³ and 14(17)-dehydrocaesalpin F (6)¹⁴ to 2-acetoxycaesaldehydine (6a)¹⁴ also been observed under this condition with excellent yields. Caesalpinin MC (5b)¹⁵ and new compound 6b were observed as the main byproducts in the aromatization processes of 5 and 6, respectively. When compounds 1–8 were dissolved in CHCl_3 and irradiated with UV light, aforementioned aromatic derivatives 2a, 3a, 5a and 6a could be produced from corresponding substrates, accompanied by the byproducts of new compound 2b and norcaesalpinin MC (2c),¹⁵ and new compound 3b and caesalmin J (3c)¹⁶ from 2 and 3, respectively. Furthermore, compounds 1–8 treated with AlCl_3 in CHCl_3 or CH_2Cl_2 could give to corresponding aromatic derivatives same as observed in CDCl_3 with excellent yields and even shorter reaction time, and the role of AlCl_3 in the aromatization of 1 has been explained by density functional theory (DFT) calculations.

Caesalmin C (2) was deacetylated with Na_2CO_3 by refluxing in MeOH for 1 h to generate 1, for which the formation was confirmed by the disappearance of acetoxy methyl signals (δ_{H} 1.97, 2.08, 2.11), carbonyl carbons (δ_{C} 169.3, 171.0, 171.0) and methyl carbons (δ_{C} 21.5, 21.6, 21.9), and proton signals of three oxygenated methines all shifted to higher fields in the NMR spectra. When 1 was dissolved in CDCl_3 , it quickly converted to 1a at room temperature (Fig. 1), as evidenced by TLC behavior and NMR data. Nevertheless, this aromatization reaction couldn't proceed in other deuterated solvents including DMSO,



CD₃OD, (CD₃)₂CO and C₅D₅N. Compound **1** was obtained as white amorphous powder, when it was dissolved in CDCl₃, the solution instantly turned pink and then became canary yellow. Compound **1a** was obtained as a white amorphous powder, and its molecular formula was deduced to be C₂₀H₂₆O₄ from the HRESIMS (*m/z* 353.1723 [M + Na]⁺, calcd 353.1729). The ¹H NMR spectrum of **1a** displayed three methyl signals (δ_{H} 1.27, s; 1.33, s; 1.34, s), a benzylic methyl signal (δ_{H} 2.41, s), two oxygenated methine signals (δ_{H} 4.52, t, *J* = 7.8 Hz; 4.55, br s), one aromatic proton (δ_{H} 7.42, s) and two protons (δ_{H} 6.75, d, *J* = 2.3 Hz; 7.55, d, *J* = 2.3 Hz) of a 1,2-disubstituted furan ring, which revealed the existence of aromatic ring. The ¹³C NMR

displayed the presence of 20 carbons including four methyls, three methylenes, five methines (three olefinic at δ_{C} 104.6, 105.2, 144.7 and two oxygenated at δ_{C} 69.7, 73.6) and eight quaternary carbons (five olefinic at δ_{C} 126.1, 128.1, 128.8, 140.0, 154.0 and one oxygenated at δ_{C} 78.5), which further supported the formation of benzene ring. The direct connections between the protons and carbons were identified by the HSQC spectrum. In the HMBC spectrum (Fig. 2), H-6 showed long-range correlation with C-7, and H₂-7 showed correlations with C-6, C-9 and C-14, indicating that the hydroxy group at C-7 in **1** has disappeared in the aromatization process. The orientation of hydroxy groups at C-1 and C-6 remained unchanged as

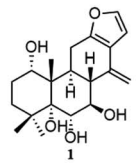
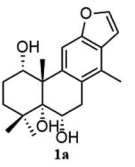
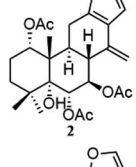
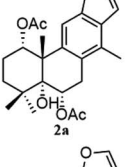
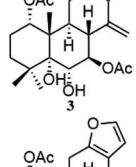
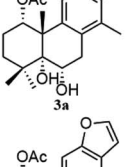
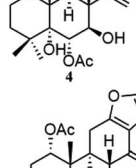
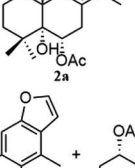
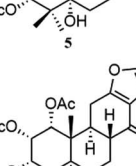
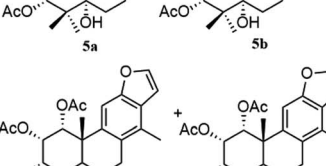
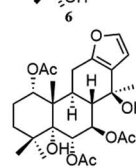
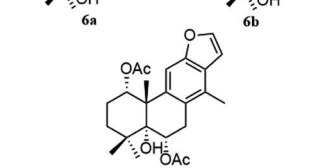
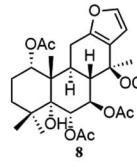
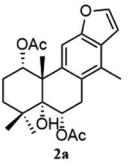
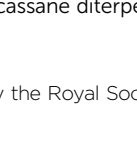
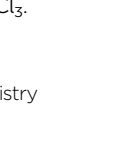
entry	cassane diterpenoids	aromatic derivatives	start time (h)	end time (h)	isolated yields (%)
1			instantly	instantly	84
2			28	120	68
3			0.75	24	72
4			0.17	4	75
5			6	60	36:34
6			6	60	34:37
7			1	192	55
8			9	240	48

Fig. 1 Scope of aromatization of cassane diterpenoids in CDCl₃.



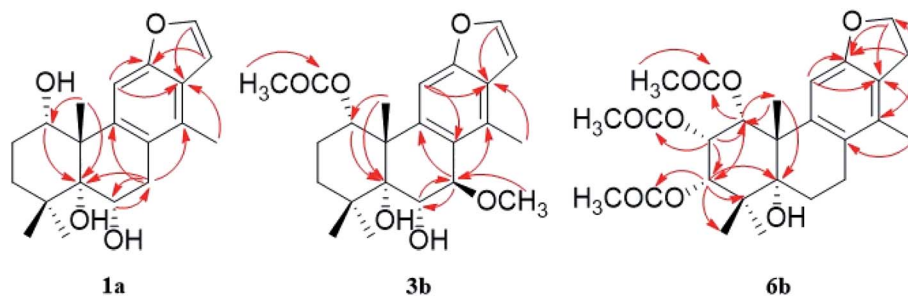


Fig. 2 Key HMBC correlations of compounds **1a**, **3b** and **6b**.

evidenced by the correlations of H-1 with H-2 α and H-2 β , and H-6 with H₃-20 in the NOESY spectrum (Fig. 3). In order to determine the absolute configuration of **1a**, the calculated ECD spectra were compared with experimental spectrum (Fig. 4), and the result showed that the calculated ECD of 1*S*,5*R*,6*S*,10*S* was consistent with experimental data of **1a**. Thus, compound **1a** was identified as 1 α ,5 α ,6 α -trihydroxy-14-methylvoucapane-8(14),9(11)-diene.

Inspired by this phenomenon, compounds **2–11**, isolated from seed kernels of *C. bonduc*, were individually dissolved in CDCl₃ to test the scope and limitations of the method. Consequently, as shown in Fig. 1, aromatic derivatives 6-acetoxy-3-deacetoxycaesaldekarin e (**2a**)⁹ from caesalmin C (**2**),⁷ bonducellpin G (**4**),⁸ caesalmin E (**7**)⁷ and caesalmin F (**8**),⁷ caesall A (**3a**)¹¹ from ζ -caesalpin (**3**),¹⁰ caesaldekarin e (**5a**)¹³ and caesalpinin MC (**5b**)¹⁵ from caesalpinin C (**5**),¹² and 2-acetoxycaesaldekarin e (**6a**)¹⁴ and **6b** from 14(17)-dehydrocaesalpin F (**6**)¹⁴ were obtained with excellent yields but the aromatization of δ -caesalpin (**9**),⁹ bonducellpin C acetate (**10**)¹⁷ and norcaesalpinin E (**11**)¹² (Fig. S1[†]) were not achieved, indicating that diene system or allylic hydroxy group and allylic methoxy group in C ring might be indispensable to the aromatization conditions. Furthermore, among diene systems, compounds decorated with homoallylic hydroxy group (**1** and **4**) were more susceptible to the aromatization process than acetyl derivatives (**2** and **3**) of the homoallylic alcohol and free counterparts (**5** and **6**). Additionally, **5** dissolved in CDCl₃ yielded a mixture of **5a** and **5b** in almost 5 : 5 ratio, similar to the case of **6**. When **7** or **8** was subjected to the same condition, the first step was the elimination of hydroxy or methoxy at C-14 to give **2** as an intermediate, and subsequently generate **2a**.

Compound **6b** was assigned as a new cassane diterpenoid. **6b** was obtained as a white amorphous powder, and its

molecular formula was established to be C₂₆H₃₄O₈ by HRESIMS analysis (m/z 497.2146 [M + Na]⁺, calcd 497.2151). The ¹H NMR spectrum displayed three methyl signals (δ_{H} 1.18, s; 1.29, s; 1.44, s), three acetoxy methyl signals (δ_{H} 1.96, s; 1.97, s; 2.11, s), a benzylic methyl signal (δ_{H} 2.13, s), two dihydrofuran methylene signals (δ_{H} 3.10, t, J = 8.6 Hz, 2H; 4.45, dt, J = 16.9, 8.6 Hz; 4.47, dt, J = 16.9, 8.6 Hz), three oxygenated methine signals (δ_{H} 5.23, d, J = 3.8 Hz; 5.69, t, J = 3.6 Hz; 5.90, d, J = 3.2 Hz) and one aromatic proton (δ_{H} 6.24, s). The ¹³C NMR spectrum revealed the presence of 26 carbons including seven methyls, four methylenes (one oxygenated at δ_{C} 71.8), four methines (one olefinic at δ_{C} 102.8 and three oxygenated at δ_{C} 68.0, 74.9, 78.2) and eleven quaternary carbons (three ester carbonyls at δ_{C} 171.4, 171.5, 171.7, five olefinic at δ_{C} 125.2, 126.6, 133.9, 143.5, 159.2 and one oxygenated at δ_{C} 77.3). The ¹H and ¹³C NMR spectra were similar to those of **5b**, except for an extra acetoxy group in **6b**, suggesting the presence of a dihydrobenzofuran fragment. The correlations of H-1 with C-10, C-20 and δ_{C} 171.4, H-2 with C-1, C-3 and δ_{C} 171.5, and H-3 with C-4, C-5, C-19 and δ_{C} 171.7 in the HMBC spectrum (Fig. 2) indicated that the acetoxy groups were attached at C-1, C-2 and C-3, respectively. The relative configuration of **6b** was determined on the basis of coupling constants and the NOESY spectrum (Fig. 3). The small coupling constants between H-1 and H-2 (3.2 Hz), and between H-2 and H-3 (3.8 Hz), and NOE correlations from H-1 to H₃-20, from H-2 to H₃-19 and H₃-20, and from H-3 to H₃-18 and H₃-19 suggested that acetoxy groups at C-1, C-2 and C-3 were all α -orientated. The absolute configuration of **6b** was determined to be 1*R*,2*S*,3*S*,5*R*,10*S* by comparing experimental ECD spectrum with calculated spectra of a pair of enantiomers (Fig. 4). Thus, the structure of **6b** was established as 1 α ,2 α ,3 α -triaceoxy-5 α -hydroxy-15,16-dihydro-14-methylvoucapane-8(14),9(11)-diene.

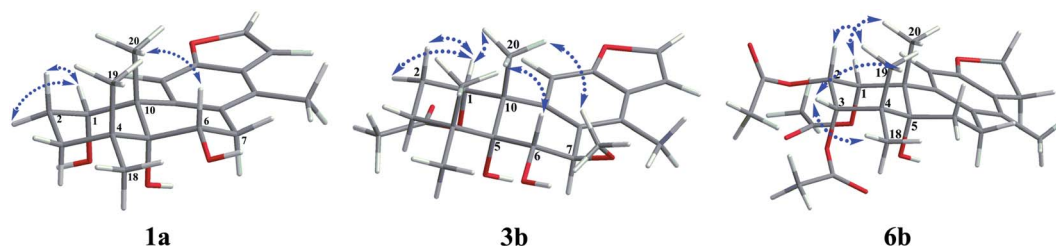


Fig. 3 Key NOESY correlations of compounds **1a**, **3b** and **6b**.



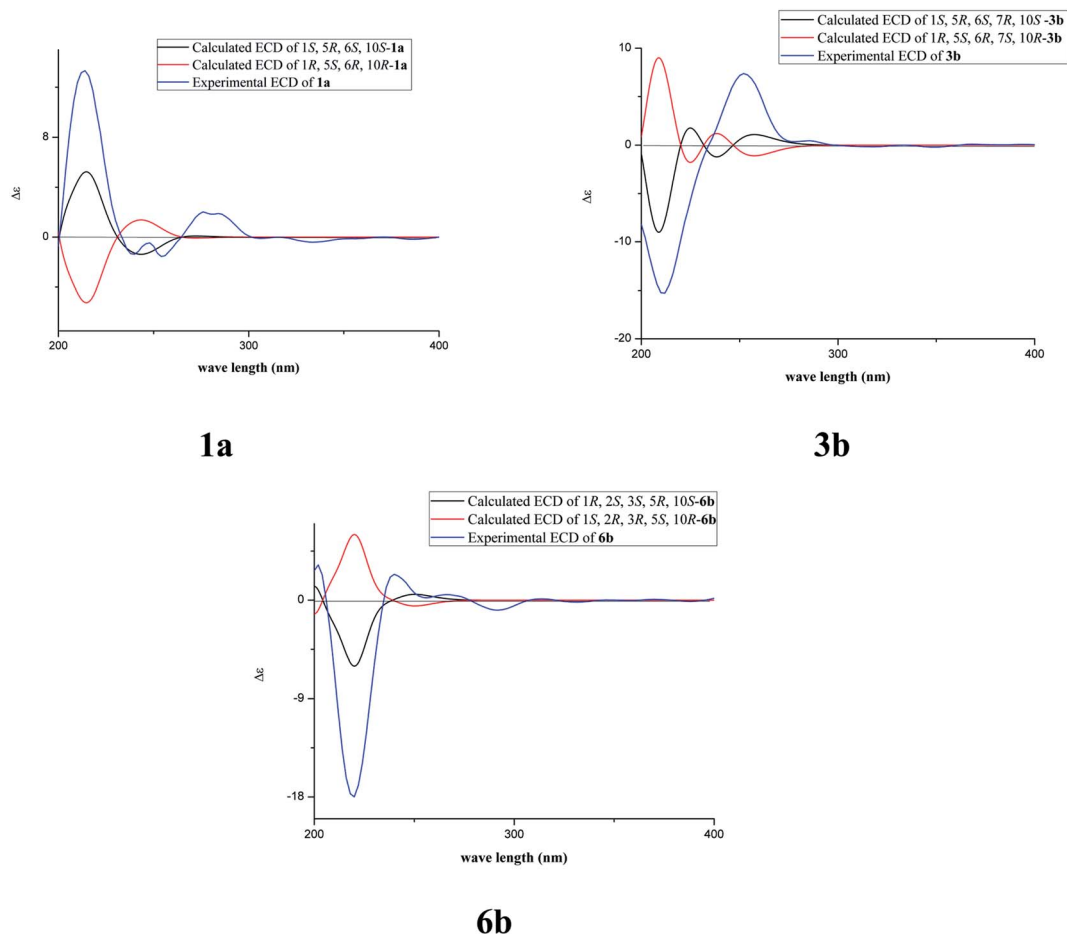


Fig. 4 Experimental and calculated ECD spectra of compounds **1a**, **3b** and **6b**.

A previous work has reported the transformation of certain biomedical compounds such as bilirubin, thymine, uracil, dehydrocholesterol and vitamin D₃ observed in deuterated solvents such as heavy water and CDCl₃, and the chemical reaction of bilirubin in CDCl₃ exhibited a striking resemblance to the photochemical reaction in CHCl₃.¹⁸ Inspired by this research, the photochemical reactions of cassane diterpenoids in CHCl₃ were explored. Gratifyingly, the photochemical reactions of cassane diterpenoids **1–8** in CHCl₃ under laboratory conditions (room temperature and exposure to UV light, 254 nm) could produce corresponding aromatic derivatives similar in CDCl₃ and other related compounds (Fig. 5). When **2** was dissolved in CHCl₃ and irradiated with UV light, aromatic derivatives **2a**, **2b** and 17-norcassane diterpenoid norcaesalpin MC (**2c**)¹⁵ were produced. The ¹H NMR and ¹³C NMR spectra of **2b** were similar to those of caesalpine D,¹⁹ except for the orientation of acetoxy group at C-7. Influenced by the rigid plane structure of benzene ring, the coupling constant between H-6 and H-7 is relatively small when the substituent groups at C-6 and C-7 were α - and β -oriented, respectively. Published compound caesalpin E²⁰ and the following **3b** have proved this point. Moreover, the orientation of substituent at C-7 remained unchanged in the photochemical reactions of **2** and **3** as evidenced by the products **2c**, **3b** and **3c**. Hence the structure of **2b**

was established as 1 α ,6 α ,7 β -triacetoxy-5 α -hydroxy-14-methylvoucapane-8(14),9(11)-diene. As shown in Fig. 5, when **3** was subjected to the same condition, **3a**, **3b** and 17-norcassane diterpenoid caesalpin J (**3c**)¹⁶ were produced. The structure of **3b** was assigned as a new cassane diterpenoid, and its molecular formula was established to be C₂₃H₃₀O₆ by HRESIMS (*m/z* 425.1935 [M + Na]⁺, calcd 425.1940). The ¹H NMR spectrum showed three methyl signals (δ_{H} 1.36, s; 1.39, s; 1.48, s), an acetoxy methyl signal (δ_{H} 1.90, s), a benzylic methyl signal (δ_{H} 2.49, s), a methoxy signal (δ_{H} 3.62, s), three oxygenated methine signals (δ_{H} 4.51, d, *J* = 4.3 Hz; 4.67, d, *J* = 4.3 Hz; 5.59, t, *J* = 3.7 Hz), one aromatic proton (δ_{H} 6.93, s) and two protons (δ_{H} 6.87, d, *J* = 2.2 Hz; 7.66, d, *J* = 2.2 Hz) of a 1,2-disubstituted furan ring. The ¹³C NMR spectrum displayed the presence of 23 carbons signals, including six methyls (one methoxy at δ_{C} 57.5), two methylenes, six methines (three olefinic at δ_{C} 104.6, 106.2, 146.2 and three oxygenated at δ_{C} 76.9, 77.3, 86.1) and nine quaternary carbons (one ester carbonyl at δ_{C} 171.5, five olefinic at δ_{C} 127.7, 130.5, 132.5, 141.5, 155.8 and one oxygenated at δ_{C} 81.0). The proton signals were assigned to the corresponding carbons through direct ¹H and ¹³C correlations in the HSQC spectrum. In the HMBC spectrum (Fig. 2), the correlations of H-1 with C-5 and δ_{C} 171.5, H-6 with C-7, H-7 with C-6, C-9 and C-14, and -OCH₃ with C-7 indicated that acetoxy, hydroxy and

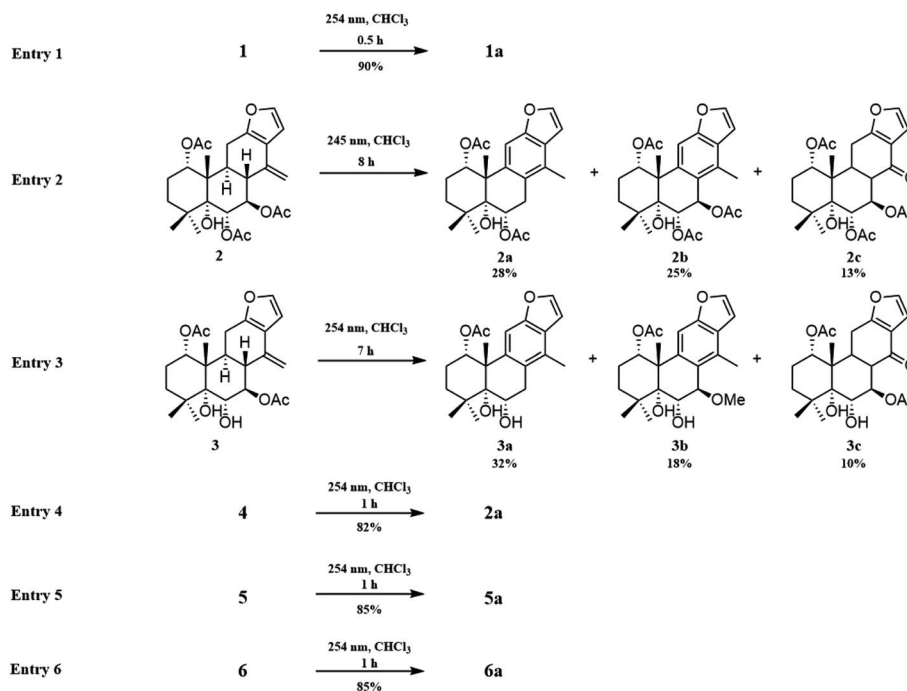


Fig. 5 Scope of aromatization of cassane diterpenoids in CHCl_3 irradiated with UV light.

methoxy groups were attached to C-1, C-6 and C-7, respectively. The relative configuration of **3b** was established through the NOESY spectrum (Fig. 3). The NOE correlations of H-1 with H-2 α , H-2 β and H₃-20, H-6 with H₃-20, and OCH₃-7 with H₃-20 suggested that acetoxy at C-1, hydroxy at C-6 and methoxy at C-7 were α -, α -, and β -oriented, respectively. Comparing the experimental ECD spectrum with calculated ECD spectra (Fig. 4) of two enantiomers, the absolute configuration of compounds **3b** and **6b** were determined to be 1*S*,5*R*,6*S*,7*R*,10*S*. Thus, compound **3b** was identified as 1 α -acetoxy-5 α ,6 α -dihydroxy-7 β -methoxy-14-methylvoucapane-8(14),9(11)-diene. As for the photochemical reactions of **7** and **8**, the first step was the elimination of hydroxy or methoxy at C-14 to yield **2**, followed by the reaction same as entry 2 (Fig. 5).

Given that CHCl_3 might have some acidic impurities such as HCl upon storage and therefore promote acid-catalyzed aromatization of these compounds, so we anticipated that some Lewis acid might involve in the aforementioned aromatization reaction. To explore this idea the compound **1** was treated with a few

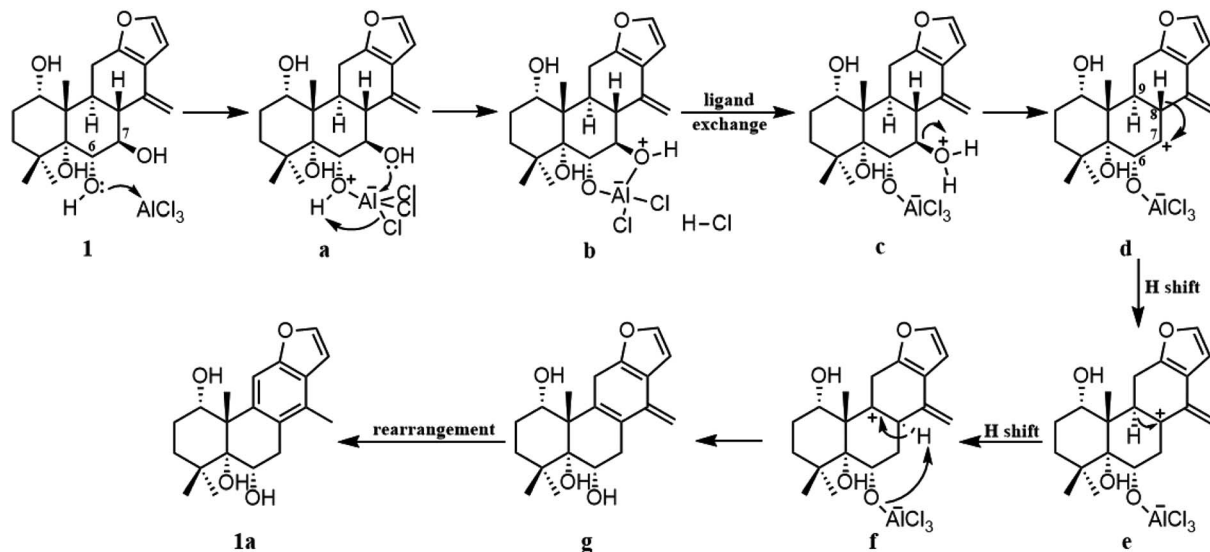
Lewis acids (AlCl_3 , FeCl_3 , ZnCl_2) in CHCl_3 at room temperature, and fortunately, the use of AlCl_3 generated the desired aromatic derivative **1a** with excellent yield. Of the solvents screened (CH_2Cl_2 , CHCl_3 , acetone, MeOH and CH_3CN), both CHCl_3 and CH_2Cl_2 could give good yields. Under the above optimized conditions, compounds **2–11** were then treated with AlCl_3 in CHCl_3 , and corresponding aromatic derivatives **2a**, **3a**, **5a**, **5b**, **6a** and the reaction time could be greatly shortened (Table 1).

To gain better insight into the mechanism for the AlCl_3 -promoted aromatization of certain cassane diterpenoid, an aromatization reaction mechanism of **1** was suggested in Scheme 1. It was proposed to start with the coordination of AlCl_3 with the oxygen atom of 6-OH to give **a**, followed by the attack of 7-OH to AlCl_3 to yield **b** and subsequent ligand exchange that generated **c** with protonation of the C-7 hydroxy group. Next, loss of the C-7 protonated hydroxy group could give **d**, and subsequent 1,2-hydride shift from C-8 to C-7 would afford the allylic carbocation **e**, which would be susceptible to

Table 1 Scope of AlCl_3 -promoted aromatization of cassane diterpenoids

Entry	Cassane diterpenoids	Aromatic derivatives	Start time (h)	End time (h)	Isolated yields
1	1	1a	Instantly	Instantly	90
2	2	2a	Instantly	0.67	82
3	3	3a	Instantly	0.08	84
4	4	2a	Instantly	0.5	85
5	5	5a + 5b	0.05	4	45 : 28
6	6	6a + 6b	0.05	4	47 : 24
7	7	2a	0.08	0.83	75
8	8	2a	0.25	1	72

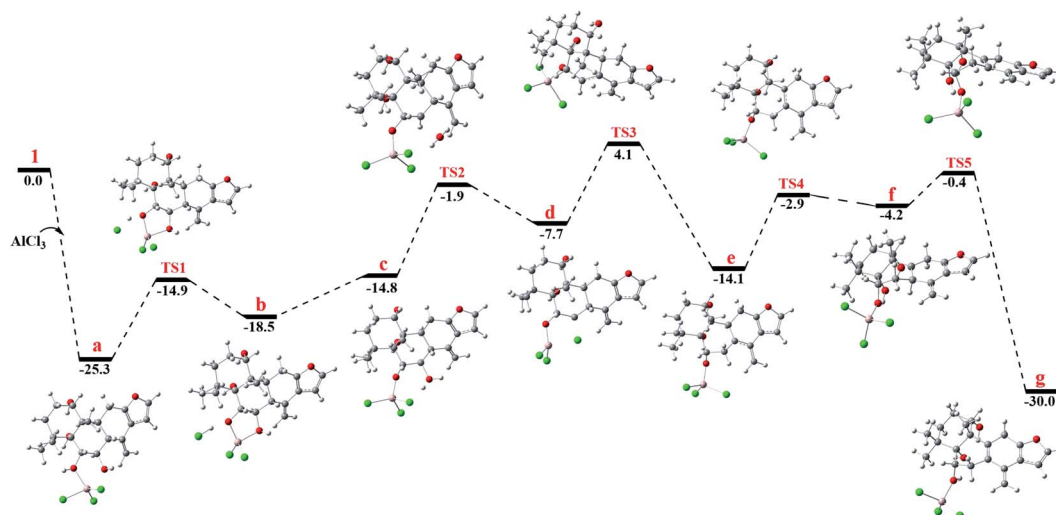


Scheme 1 Putative mechanism for the AlCl_3 -mediated aromatization of **1**.

a further 1,2-hydride shift from C-9 to C-8 to afford **f**, making it easy to the formation of **g** with triene fragment in C ring. Finally, the rearrangement of double bond would provide the aromatic derivative **1a**. The above route about AlCl_3 -promoted formation of triene **g** is supported by DFT calculations at B3LYP/6-31G (d,p). As shown in Fig. 6, AlCl_3 coordinated with hydroxy group at C-6 in **1** to give intermediate **a**, which is more stable than **1** by 25.3 kcal mol⁻¹, suggesting this complexation process are spontaneous. Then, attack of C-7 hydroxy on AlCl_3 took place through transition state **TS1** to give intermediate **b** with an activation free energy of 10.4 kcal mol⁻¹ relative to **a**. This was followed by the ligand exchange and dehydration *via* intermediate **c** and transition state **TS2** to generate **d**. The barrier for this step was calculated to be 16.6 kcal mol⁻¹, which is 1.9 kcal mol⁻¹ lower compared to **1**. Subsequently, **d** was converted to **f** through twice 1,2-hydride shift *via* transition states

TS3, **TS4** and allylic carbocation intermediate **e**. The free energy barrier for twice hydride shift were calculated to be 11.8 and 11.2 kcal mol⁻¹, respectively. Finally, **g** equipped with triene segment in C ring was formed through transition state **TS5** with a barrier of 3.8 kcal mol⁻¹. The above-mentioned results indicated that the rate-limiting step of the above reaction proceeds through transition state **TS2** with a barrier of 16.6 kcal mol⁻¹, and **TS2** is more stable than **1** by 1.9 kcal mol⁻¹, so above reaction could happen easily at room temperature.

For the mechanism described above, it is reasonable for compounds **1–4**, **7** and **8**. As for compound **5** or **6**, the absence of 7-oxy function led to more difficult aromatization of C ring compared to compounds **1–4**, presumably there is no obvious leaving group, which is needed for the formation of carbocation or unsaturated double bond, and longer reaction time also provided evidence to support this. On the other hand, the

Fig. 6 The free energy profile for the aromatization of **1** promoted by AlCl_3 .

dehydrogenation of diene in C ring of compound **5** or **6** might be due to air oxidation in the presence of AlCl_3 , and stabilization of **5** or **6** could be the driving force in losing the hydrogen by air oxidation to form the aromatic derivative **5a** or **6a**.²¹ Furthermore, compared with compound **5** or **6**, degree of unsaturation and chemical formula of side product **5b** or **6b** remained unchanged, prompting that acid-induced rearrangement took place, and consequently the molecular was fully delocalized and conjugated. Further studies however are required to verify the mechanism proposed above.

In the photochemical reactions of compounds **2** and **3**, besides compounds **2a** and **3a**, aromatic derivatives **2b** and **3b**, and oxidative products **2c** and **3c** also been obtained. We speculated that they may be generated through photo-induced aromatization and oxidation owing to the existence of double bond between C-14 and C-17, and research is continuing to confirm the exact reaction mechanism.

4 Conclusions

In this study, three methods of aromatizing several cassane diterpenoids were described. The aromatization of cassane diterpenoids occurred in CDCl_3 reminded us that deuterated solvents display somewhat different chemical nature with their ordinary counterparts and may contribute to the transformation of specific compounds. For natural products researchers, particular attention should be paid to this point. The photochemical reactions of cassane diterpenoids reported in this study also provided us with new prospective of influence of UV light on the natural products. Additionally, compounds **2a**, **2c**, **3a**, **3c**, **5a**, **5b** and **6a** have been isolated from plants of *Caesalpinia* genus, revealing that several biochemical processes may be related to laboratory studies. The chemical transformations reported here would provide information related to the possible biogenesis of these diterpenoids and could be useful for the synthesis of these biologically interesting compounds.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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