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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 *[ab]

Transformations of cassane diterpenoids from *Caesalpinia bonduc* into aromatic derivatives, either in $CDCl_3$ or in $CHCl_3$ irradiated with UV light or catalyzed by $AlCl_3$, were described. Caesalmin C (**2**) was hydrolyzed with Na_2CO_3 upon refluxing in MeOH to yield compound **1**. Dissolving compound **1** with $CDCl_3$ resulted in an unexpected aromatization process of a C ring to obtain **1a**, and aromatic derivatives 6-acetoxy-3-deacetoxycaesaldekarin e (**2a**), caesall A (**3a**), caesaldekarin e (**5a**), caesalpinin MC (**5b**), 2-acetoxycaesaldekarin e (**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 $CHCl_3$ also yielded aromatic derivatives **1a**, **2a**, **3a**, **5a**, **6a**, new compounds **2b** and **3b**, and 17-norcassane diterpenoids norcaesalpinin MC (**2c**) and caesalmin J (**3c**). In addition, cassane diterpenoids **1–8**, treated with $AlCl_3$ in $CHCl_3$ or CH_2Cl_2, gave the same results in $CDCl_3$ and with even shorter reaction time. The role of $AlCl_3$ 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 benthaminin 1,[2] taepeenin D,[3] taepeenin F,[4] (5α)-vouacapane-8(14),9(11)-diene,[5] sucutinirane C and sucutiniran D[6] from commercially available materials. In this paper the transformation of cassane-type diterpenoids with a fused furan ring into aromatic derivatives in $CDCl_3$, or upon irradiation with UV light in $CHCl_3$, or catalyzed by $AlCl_3$ in $CHCl_3$ or CH_2Cl_2 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 (GF_{254}) 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 μm, 20 × 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

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

[b]*Key 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–H_2O (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–H_2O (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–H_2O (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–H_2O (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 × 2) and saturated NaCl (5 mL × 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–H_2O (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–H_2O (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 × 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 1α,5α,6α,7β-Tetrahydroxyvoucapane-14(17)-ene (1). White amorphous powder; ^{1}H 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, H_3-19), 1.26 (3H, s, H_3-18), 1.10 (3H, s, H_3-20), 1.01 (1H, m, H-3); ^{13}C 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 (CH_2, 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 (CH_2, C-3), 32.1 (CH_3, C-18), 26.4 (CH_2, C-11), 25.8 (CH_3, C-19), 23.9 (CH_2, C-2), 17.2 (CH_3, C-20); HRESIMS m/z 371.1829 $[M + Na]^+$ (calcd for $C_{20}H_{28}O_5Na$, 371.1834).

2.8.2 1α,5α,6α-Trihydroxy-14-methylvoucapane-8(14),9(11)-diene (1a). White amorphous powder; $[\alpha]_D^{20}$ +25 (c 0.25, MeOH); ECD (MeOH) λ_{max} ($\Delta\varepsilon$) 214 (+13.32), 254 (−1.55), 276 (+2.02) nm; ^{1}H 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, H_3-17), 2.18 (1H, m, H-2), 2.14 (1H, m, H-3), 1.94 (1H, m, H-2), 1.34 (3H, s, H_3-18), 1.33 (3H, s, H_3-19), 1.27 (3H, s, H_3-20), 1.18 (1H, m, H-3); ^{13}C 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 (CH_2, C-7), 32.4 (CH_2, C-3), 30.9 (CH_3, C-18), 28.8 (CH_3, C-20), 25.2 (CH_3, C-19), 25.1 (CH_2, C-2), 16.1 (CH_3, C-17); HRESIMS m/z 353.1723 $[M + Na]^+$ (calcd for $C_{20}H_{26}O_4Na$, 353.1729).

2.8.3 5α-Hydroxy-1α,6α,7β-trihydroxy-14-methylvoucapane-8(14),9(11)-diene (2b). White amorphous powder; ^{1}H 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, H_3-17), 2.21 (1H, m, H-2), 2.13 (3H, s, 6-OCOCH_3), 2.02 (3H, s, 7-OCOCH_3), 1.97 (1H, m, H-3), 1.90 (3H, s, 1-OCOCH_3), 1.89 (1H, m, H-2), 1.59 (3H, s, H_3-20), 1.24 (3H, s, H_3-18), 1.22 (3H, s, H_3-19), 1.19 (1H, m, H-3); ^{13}C NMR (150 MHz, CD_3OD) δ 172.8 (C, 6-O<u>C</u>OCH_3), 172.5 (C, 7-O<u>C</u>OCH_3), 171.2 (C, 1-O<u>C</u>OCH_3), 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 (CH_2, C-3), 30.8 (CH_3, C-18), 29.3 (CH_3, C-20), 25.2 (CH_3, C-19), 23.4 (CH_2, C-2), 22.0 (CH_3, 6-OCO<u>C</u>H_3), 21.1 (CH_3, 7-OCO<u>C</u>H_3), 21.0 (CH_3, 1-OCO<u>C</u>H_3), 16.1 (CH_3, C-17); HRESIMS m/z 495.1989 $[M + Na]^+$ (calcd for $C_{26}H_{32}O_8Na$, 495.1995).

2.8.4 1α-Acetoxy-5α,6α-dihydroxy-7β-methoxy-14-methylvoucapane-8(14),9(11)-diene (3b). White amorphous powder; $[\alpha]D^{20}$ +8 (c 0.22, MeOH); ECD (MeOH) λ_{max} ($\Delta\varepsilon$) 212 (−15.27), 252 (7.38) nm; ^{1}H 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-OCH_3), 2.49 (3H, s, H_3-17), 2.19 (1H, m, H-2), 1.97 (1H, m, H-3), 1.90 (3H, s, 1-OCOCH_3), 1.86 (1H, m, H-2), 1.48 (3H, s, H_3-20), 1.39 (3H, s, H_3-19), 1.36 (3H, s, H_3-18), 1.15 (1H, m, H-3); ^{13}C NMR (150 MHz, CD_3OD) δ 171.5 (C, 1-O<u>C</u>OCH_3), 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 (CH_3, 7-OCH_3), 49.1 (C, C-10), 40.0 (C, C-4), 33.9 (CH_2, C-3), 31.3 (CH_3, C-18), 29.0 (CH_3, C-20), 25.9 (CH_3, C-19), 23.6 (CH_2, C-2), 21.1, (CH_3, 1-OCO<u>C</u>H_3), 16.2 (CH_3, C-17); HRESIMS m/z 425.1935 $[M + Na]^+$ (calcd for $C_{23}H_{30}O_6Na$, 425.1940).

2.8.5 1α,2α,3α-Triacetoxy-5α-hydroxy-15,16-dihydro-14-methylvoucapane-8(14),9(11)-diene (6b). White amorphous powder; $[\alpha]_D$20 −48 (c 0.23, MeOH); ECD (MeOH) λ_{max} ($\Delta\varepsilon$) 220 (−17.99), 240 (2.37) nm; ^{1}H 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, H_2-15), 2.75 (1H, m, H-7), 2.67 (1H, m, H-7), 2.13 (3H, s, H_3-17), 2.11 (3H, s, 3-OCOCH_3), 2.09 (1H, m, H-6), 2.01 (1H, m, H-6), 1.97 (3H, s, 2-OCOCH_3), 1.96 (3H, s, 1-OCOCH_3), 1.44 (3H, s, H_3-20), 1.29 (3H, s, H_3-19), 1.18 (3H, s, H_3-18); ^{13}C NMR (150 MHz, CD_3OD) δ 171.7 (C, 3-O<u>C</u>OCH_3), 171.5 (C, 2-O<u>C</u>OCH_3), 171.3 (C, 1-O<u>C</u>OCH_3), 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 (CH_2, C-16), 68.0 (CH, C-2), 49.3 (C, C-10), 44.0 (C, C-4), 31.1 (CH_3, C-20), 29.9 (CH_2, C-15), 25.4 (CH_3, C-19), 25.3 (CH_2, C-6), 24.2 (CH_2, C-7), 23.5 (CH_3, C-18), 21.0, (CH_3, 1-OCO<u>C</u>H_3), 20.9, (CH_3, 3-OCO<u>C</u>H_3), 20.6, (CH_3, 2-O<u>C</u>OCH_3), 16.3 (CH_3, C-17); HRESIMS m/z 497.2146 $[M + Na]^+$ (calcd for $C_{26}H_{34}O_8Na$, 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-deacetoxycaesaldekarin e (**2a**),[9] ζ-caesalpin (**3**)[10] to caesall A (**3a**),[11] caesalpinin C (**5**)[12] to caesaldekarin e (**5a**),[13] and 14(17)-dehydrocaesalpin F (**6**)[14] to 2-acetoxycaesaldekarin e (**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,

CD_3OD, $(CD_3)_2CO$ and C_5D_5N. Compound **1** was obtained as white amorphous powder, when it was dissolved in $CDCl_3$, the solution instantly turned pink and them became canary yellow. Compound **1a** was obtained as a white amorphous power, and its molecular formula was deduced to be $C_{20}H_{26}O_4$ 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 ^{13}C 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 olefinc 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 H_2-7 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

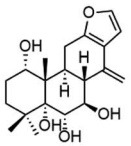
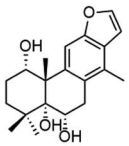
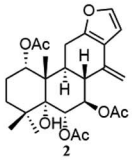
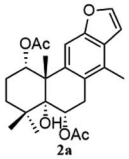
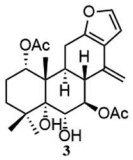
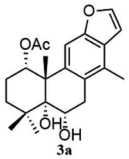
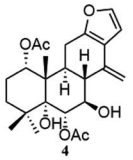
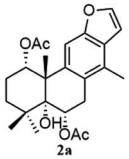
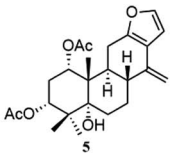
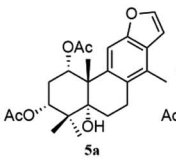
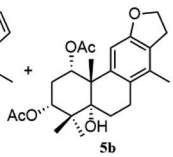
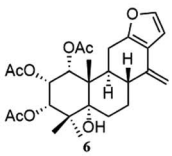
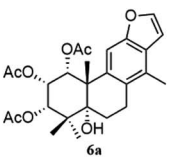
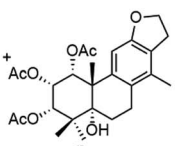
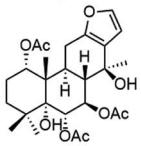
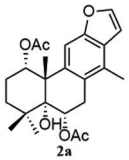
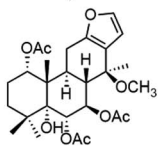
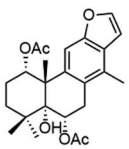
entry	cassane diterpenoids	aromatic derivatives	start time (h)	end time (h)	isolated yields (%)
1	 1	 1a	instantly	instantly	84
2	 2	 2a	28	120	68
3	 3	 3a	0.75	24	72
4	 4	 2a	0.17	4	75
5	 5	 5a +  5b	6	60	36:34
6	 6	 6a +  6b	6	60	34:37
7	 7	 2a	1	192	55
8	 8	 2a	9	240	48

Fig. 1 Scope of aromatization of cassane diterpenoids in $CDCl_3$.

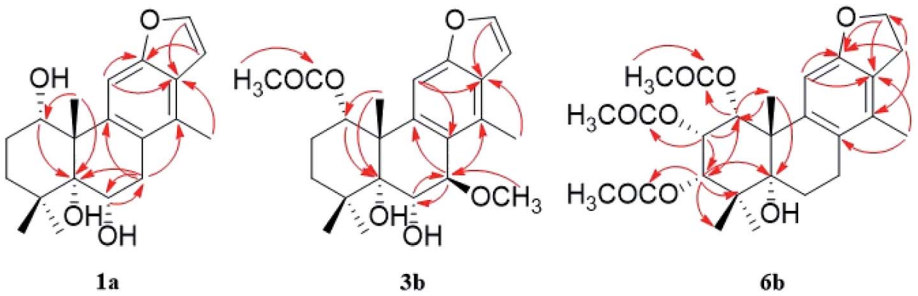


Fig. 2 Key HMBC correlations of compounds **1a**, **3b** and **6b**.

evidenced by the correlations of H-1 with H-2α and H-2β, and H-6 with H_3-20 in the NOESY spectrum (Fig. 3). In order to determine the absolute configuration of **1a**, the calculated ECD spectra were compared with experimental spe-ctrum (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 1α,5α,6α-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 $CDCl_3$ to test the scope and limitations of the method. Consequently, as shown in Fig. 1, aromatic derivatives 6-acetoxy-3-deacteoxycaesaldekarin 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 $CDCl_3$ 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 $C_{26}H_{34}O_8$ 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 ^{13}C 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 ^{13}C 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 H_3-20, from H-2 to H_3-19 and H_3-20, and from H-3 to H_3-18 and H_3-19 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 1α,2α,3α-triacetoxy-5α-hydroxy-15,16-dihydro-14-methylvoucapane-8(14),9(11)-diene.

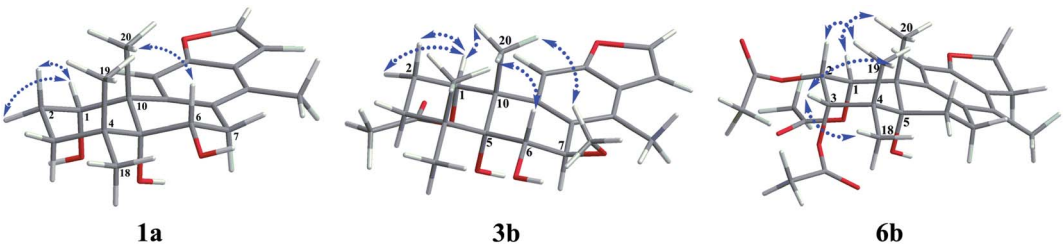


Fig. 3 Key NOESY correlations of compounds **1a**, **3b** and **6b**.

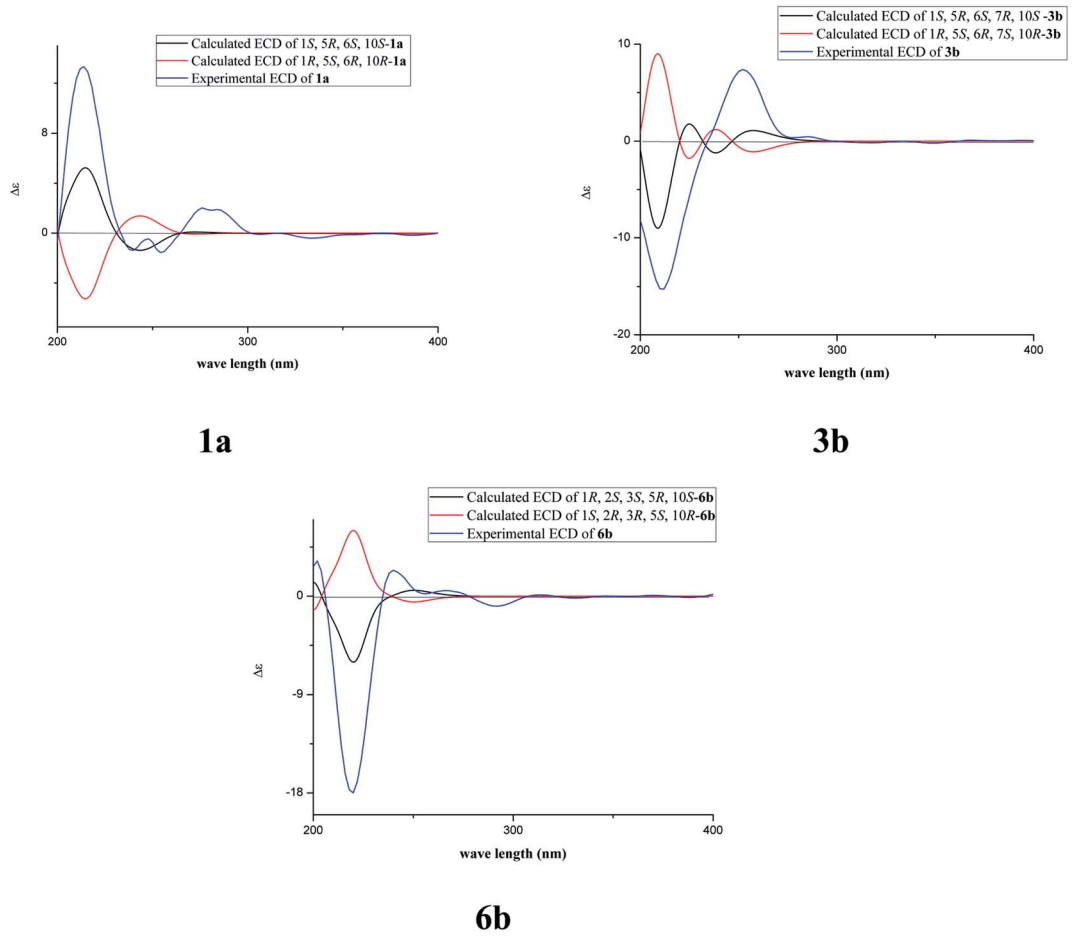


Fig. 4 Experimental and calculated ECD spectra of compounds **1a**, **3b** and **6b**.

A previous work has reported the transformation of certain biomedical compounds such as bilirubin, thymine, uracil, dehydrocholesterol and vitamin D_3 observed in deuterated solvents such as heavy water and $CDCl_3$, and the chemical reaction of bilirubin in $CDCl_3$ exhibited a striking resemblance to the photochemical reaction in $CHCl_3$.[18] Inspired by this research, the photochemical reactions of cassane diterpenoids in $CHCl_3$ were explored. Gratifyingly, the photochemical reactions of cassane diterpenoids **1–8** in $CHCl_3$ under laboratory conditions (room temperature and exposure to UV light, 254 nm) could produce corresponding aromatic derivatives similar in $CDCl_3$ and other related compounds (Fig. 5). When **2** was dissolved in $CHCl_3$ and irradiated with UV light, aromatic derivatives **2a**, **2b** and 17-norcassane diterpenoid norcaesalpinin MC (**2c**)[15] were produced. The ^{1}H NMR and ^{13}C 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 E[20] 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 1α,6α,7β-triacetoxy-5α-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 caesalmin J (**3c**)[16] were produced. The structure of **3b** was assigned as a new cassane diterpenoid, and its molecular formula was established to be $C_{23}H_{30}O_6$ by HRESIMS (m/z 425.1935 $[M + Na]^+$, calcd 425.1940). The ^{1}H 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 ^{13}C 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 ^{1}H and ^{13}C 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 –OCH_3 with C-7 indicated that acetoxy, hydroxy and

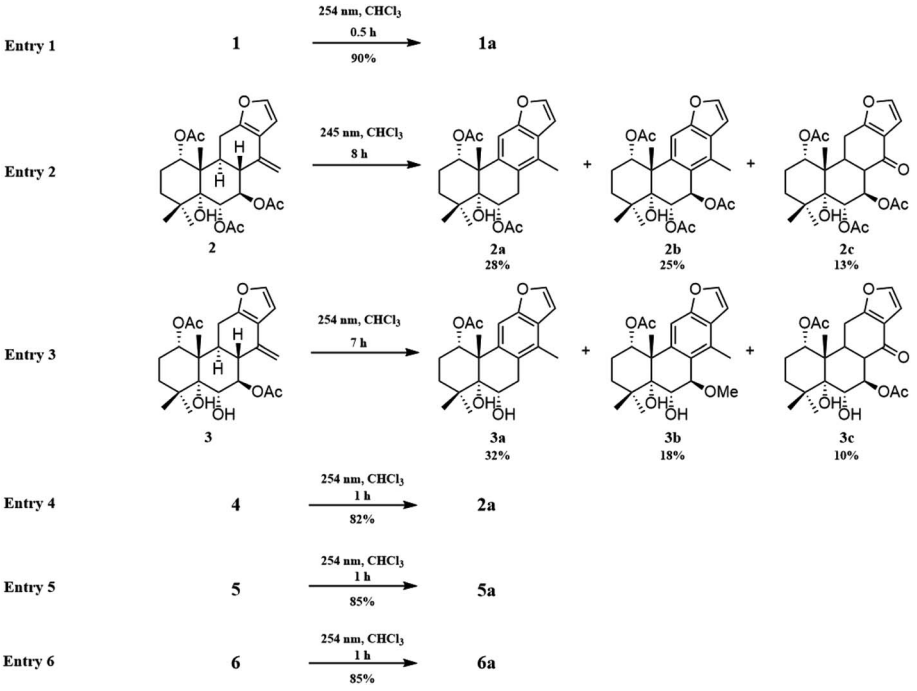


Fig. 5 Scope of aromatization of cassane diterpenoids in $CHCl_3$ irradiated with UV light.

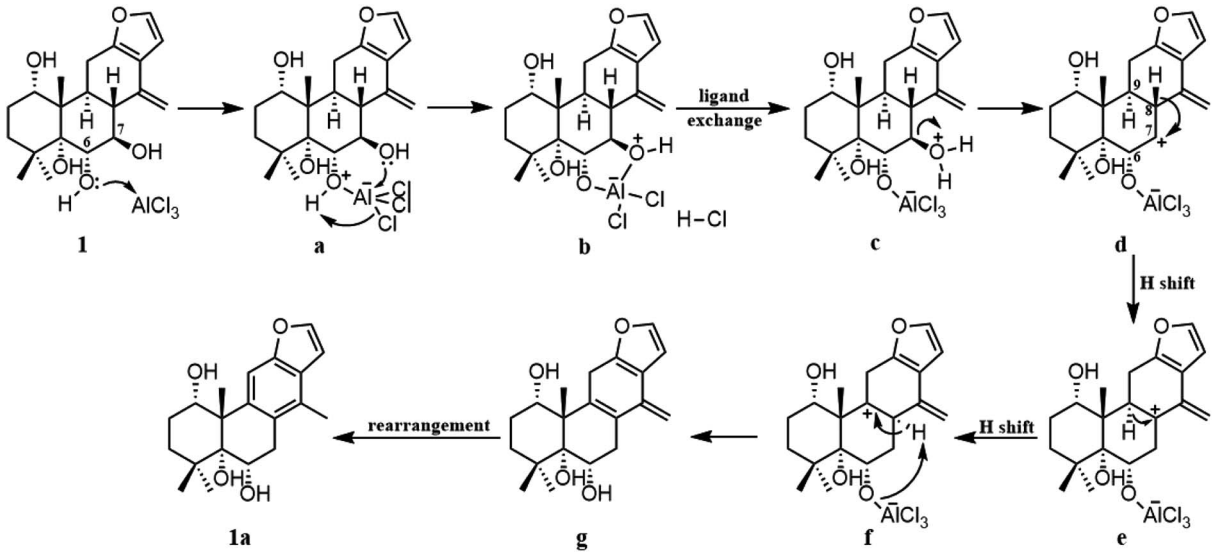
methoxy groups were attached to C-1, C-6 and C-7, respectively. The relative configuration of **3b** was established through the NOESY spectrum (Fig. 3). The NOE correlations of H-1 with H-2α, H-2β and H_3-20, H-6 with H_3-20, and OCH_3-7 with H_3-20 suggested that acetoxy at C-1, hydroxy at C-6 and 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** were determined to be 1*S*,5*R*,6*S*,7*R*,10*S*. Thus, compound **3b** was identified as 1α-acetoxy-5α,6α-dihydroxy-7β-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 gave 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 **6b** were obtained from compounds **2–8** in good yields, 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

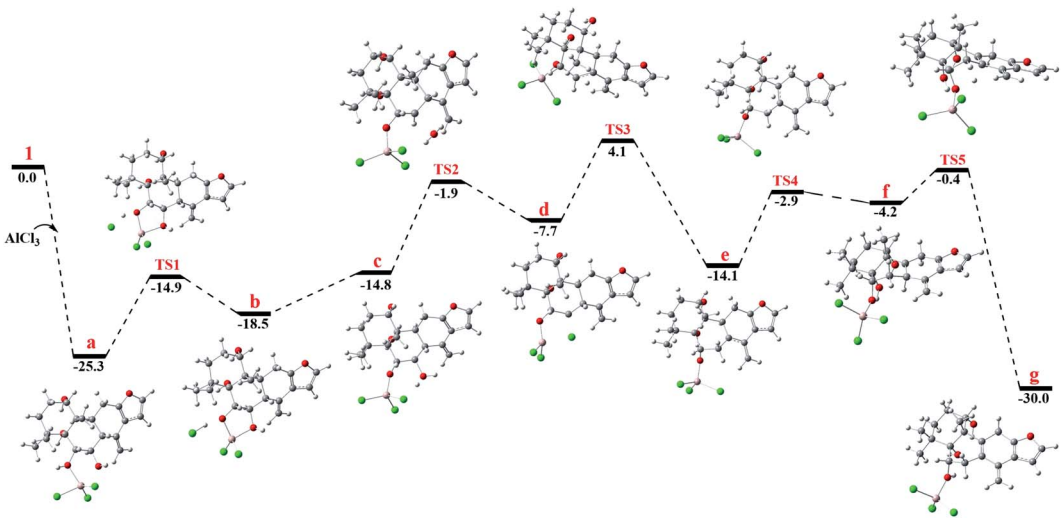


Fig. 6 The free energy profile for the aromatization of **1** promoted by $AlCl_3$.

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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