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Chemical transformation of inocalophyllins, preparation of novel pyranocoumarines inocalocyclides

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Abstract—Lactonization of inocalophyllins A (**5**) and B (**6**) with toluenesulfonic acid has yielded four novel pyranocoumarins, designated inocalocyclides A–D (**1**–**4**). This reaction involved a rare elimination of an isoprene unit and an ene cyclization.

Calanolides and inophyllums are novel non-nucleoside inhibitors of HIV type 1 reverse transcriptase.[1–4] Calanolides may be promising candidates for combination therapy with either the nucleoside AZT and/or protease inhibitors in HIV patients. It is quite urgent to search for a renewable and economic source of calanolides. Inocalophyllins A (**5**) and B (**6**) were two novel pyranocoumarins recently isolated from the seeds of *Calophyllum inophyllum* (Hypericaceae).[5,6] They represented a new class of pyranocoumarin derivatives, which contain an isoprene unit and a monoterpene group at C-8a position of the unique pyranocoumarin ring system. Lactonization at C-2 carboxylic acid would provide compounds whose structures are more similar to calanolides. In our attempt to modify the structures of the natural products **5** and **6**, we unexpectedly discovered some interesting reaction products **1**–**4** by lactonization of **5** and **6**.

Treatment of **6** with toluenesulfonic acid in toluene at 80 °C for 5 h provided inocalocyclide A (**1**) in 30% yield (Scheme 1). However, the reaction products would be compounds **2** and **3**, respectively, from **5** and **6** at 110 °C. The former reaction involved elimination of 3,3-dimethylpropenyl moiety at C-7 and lactonization between C-2 acidic group and C-6 protonated hydroxyl group. The latter reaction is an ene cyclization between double bonds of C-27 and C-28. Upon acetylation, inocalocyclide A (**1**) yielded **4**.[10] Compounds **1**–**4** represent a new class of prenylated pyranocoumarins having a monoterpene side chain at C-7.

Inocalocyclide A (**1**),[7] $[\alpha]_D$ −12° (CH_2Cl_2), was obtained as an amorphous solid. The molecular formula of **1** ($C_{27}H_{36}O_5$) was deduced from a quasimolecular ion at m/z 441 in the FABMS and ^{13}C NMR spectra. The ^1H NMR spectrum displayed signals for a phenolic proton (δ 12.2s), three olefinic protons (δ 5.05, 4.42, 4.57), three olefinic methyl singlets (δ 1.70, 1.54, and 1.66), and two methyl doublets at δ 1.21 (Me-22) and at δ 1.50 (Me-21). The ^{13}C NMR spectrum of **1** exhibited signals for a conjugated ketone carbonyl (δ 200.1), a lactone carbonyl (δ 167.4), and 10 sp^2 carbons, of which three are oxygenated quarternaries (δ 156.6, 158.6, 157.4). The structure of **1** was deduced using COSY, HSQC, and HMBC experiments. (Fig. 1) The H-4 (δ 3.34) was correlated with carbons at δ 106.9 (C-5), 156.6 (C-6). In the meanwhile, the methylene protons at δ 2.65 (C-23) were correlated to C-6 and C-7 (δ 108.2). The COSY correlations between H-23/H-24, H-24/H-25, and H-25/H-26 as well as HMBC correlations between C-26/H-31, H-32, and H-24 in addition to H-24/C-28 and C-30 allowed the assignment of the monoterpene side chain at C-7.

Inocalocyclide B (**2**),[8] $[\alpha]_D$ −18.5° (CH_2Cl_2), had the same molecular formula $C_{27}H_{36}O_5$ as **1**. The ^1H and ^{13}C NMR spectral data of **2** resembled those of **1** except for the absence of signals attributable to the olefinic methylene and methine at C-26 and C-28, respectively. Detailed analysis of the HMBC data revealed that **2** contains a 2,4,4-trimethyl cyclohexene moiety. The

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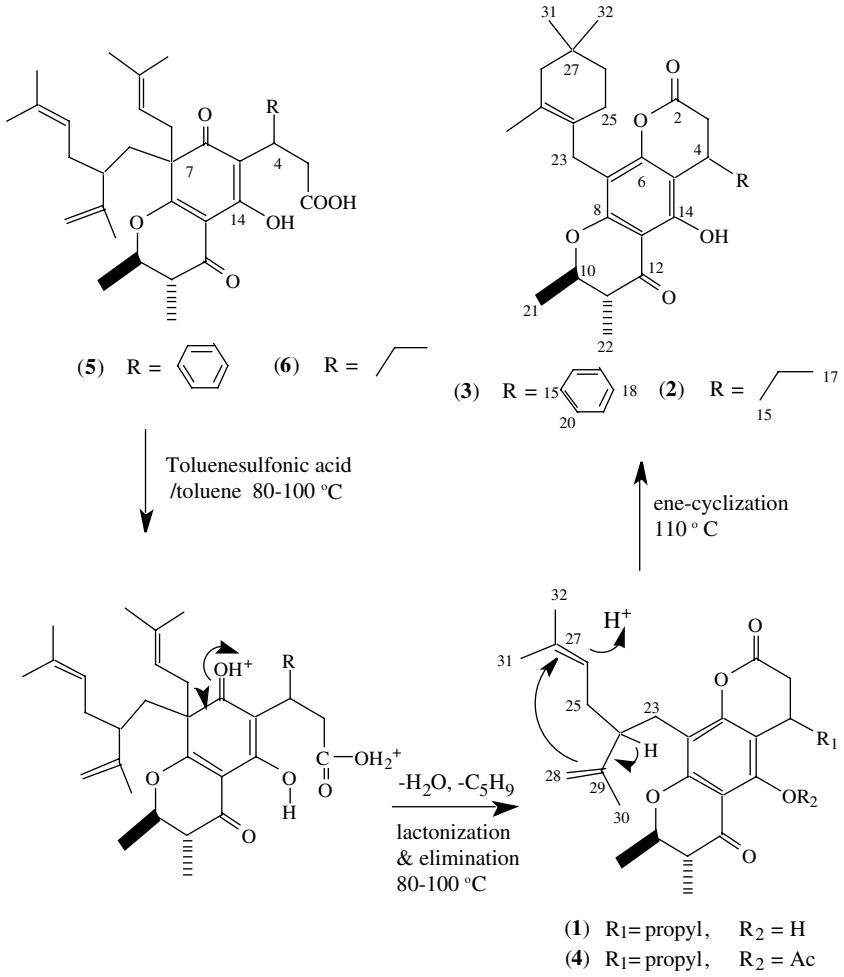

Scheme 1. Chemical transformation of **5** and **6** to inocalocyclides (**1**–**4**).

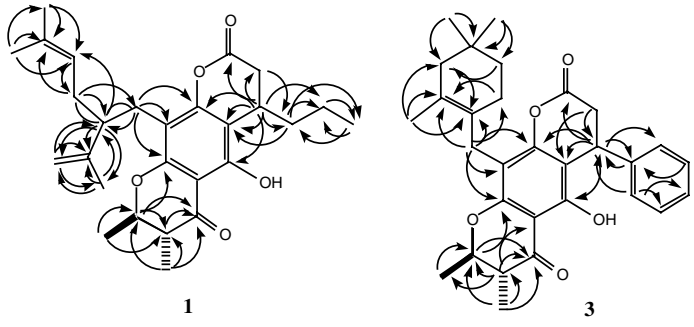

Figure 1. HMBC of inocalocyclides A (**1**) and C (**3**).

methyl singlet at δ 1.78 (Me-30) was correlated to the olefinic carbons at δ 126.1, 125.5 (C-24, 29), and the methylene carbon at δ 45.8 (C-28), which was also correlated with the methyl protons at δ 0.80 (H-31). All the other spectral data of **2** agreed with the structural assignment of inocalocyclide B.

Inocalocyclide C (**3**),[9] $[\alpha]_D$ −60° (CH_2Cl_2), was obtained as an amorphous solid. The ^1H and ^{13}C NMR data of **3** were superimposable with those of **2** except that **3** contained an extra phenyl moiety (δ 7.18–7.28) and corresponding carbon signals (δ 140.9s, 126.7d, 127.3d, 128.9d), suggesting that it was a close analogue of **2**. The structure of **3** was confirmed by HMBC experiment (Fig. 1), in which the H-4 (δ 4.66) was correlated with carbons at δ 166.4 (C-2), 105.1 (C-5), 106.9 (C-15), 126.7 (C-16), and 156.8 (C-14). Furthermore, HMBC correlations in the 2,4,4-trimethyl cyclohexene moiety were

also observed. The similar chemical shifts, coupling constants, and specific rotation of **1**–**4** were suggestive of their identical stereochemistry.

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7. Inocalocyclide A (**1**): $[\alpha]_D^{25}$ −12° (*c* 1.0, CH_2Cl_2); UV λ_{max} (MeOH) nm: 240, 276, 285, 303, 332; IR (neat) ν_{max} 3058, 1779, 1633, 1449, 1378, 1269 cm^{-1}; FABMS *m/z*: 441 $[M+H]^+$; EIMS *m/z* (rel int) 440 $[M]^+$, 317, 275, 233, 219, 217, 177, 123, 109, 81, 69; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.50 (1H, m, H-3A), 2.70 (1H, m, H-3B), 3.34 (1H, m, H-4), 4.15 (1H, m, H-10), 2.55 (1H, m, H-11), 1.45 (1H, m, H-15), 1.50 (1H, m, H-16), 0.88 (t, $J = 6.9$ Hz, H-17), 1.48 (3H, d, $J = 6.3$ Hz, H-21), 1.21 (1H, d, $J = 6.9$ Hz, H-22), 2.65 (2H, m, H-23), 2.35 (1H, m, H-24), 2.10 (2H, m, H-25), 5.05 (1H, t, $J = 8$ Hz, H-26), 4.42 (1H, d, $J = 2.1$ Hz, H-28A), 4.57 (1H, s, H-28B), 1.70 (3H, s, H-30), 1.54 (3H, s, H-31), 1.66 (3H, s, H-32), 12.2 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.4 (s, C-2), 34.1 (t, C-3), 28.2 (d, C-4), 106.9 (s, C-5), 156.6 (s, C-6), 108.2 (s, C-7), 158.6 (s, C-8), 79.0 (d, C-10), 46.1 (d, C-11), 200.1 (s, C-12), 103.9 (s, C-13), 157.4 (s, C-14), 36.4 (t, C-15), 19.8 (t, C-16), 14.0 (q, C-17), 19.6 (q, C-21), 10.0 (q, C-22), 26.7 (t, C-23), 47.7 (d, C-24), 31.4 (t, C-25), 123.1 (d, C-26), 131.1 (s, C-27), 111.2 (t, C-28), 147.7 (s, C-29), 18.7 (q, C-30), 17.9 (q, C-31), 25.7 (q, C-32).
8. Inocalocyclide B (**2**): $[\alpha]_D^{25}$ −18.5° (*c* 1.0, CH_2Cl_2); UV λ_{max} (MeOH) nm: 257, 268, 300, 350; IR (neat) ν_{max} 1779, 1634, 1450, 1381, 737 cm^{-1}; EIMS *m/z* (rel int) 440 $[M]^+$, 372, 371, 331, 318, 317, 275, 233, 219, 217, 177, 123, 109, 84, 81, 69; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.84 (1H, m, H-3A), 2.78 (1H, m, H-3B), 3.37 (1H, m, H-4), 4.19 (1H, m, H-10), 2.58 (1H, m, H-11), 1.22 (1H, m, H-15), 1.21 (1H, m, H-16), 0.89 (t, $J = 7.2$ Hz, H-17), 1.50 (3H, d, $J = 6.6$ Hz, H-21), 1.20 (1H, d, $J = 6.9$ Hz, H-22), 3.48 (1H, s, H-23), 1.78 (2H, m, H-25), 1.31 (2H, m, H-26), 1.74 (2H, s, H-28), 1.78 (3H, s, H-30), 0.80 (3H, s, H-31), 0.81 (3H, s, H-32), 12.3 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.7 (s, C-2), 34.1 (t, C-3), 29.1 (d, C-4), 111.1 (s, C-5), 156.8 (s, C-6), 113.8 (s, C-7), 158.9 (s, C-8), 79.4 (d, C-10), 46.6 (d, C-11), 199.8 (s, C-12), 108.1 (s, 13), 156.8 (s, C-14), 35.9 (t, C-15), 20.0 (t, C-16), 14.1 (q, C-17), 19.6 (q, C-21), 10.1 (q, C-22), 25.6 (t, C-23), 126.1 (d, C-24), 25.9 (t, C-25), 35.4 (d, C-26), 29.1 (s, C-27), 45.8 (t, C-28), 125.5 (s, C-29), 18.9 (q, C-30), 28.1 (q, C-31, 32).
9. Inocalocyclide C (**3**): $[\alpha]_D^{25}$ −60° (*c* 1.0, CH_2Cl_2); UV λ_{max} (MeOH) nm: 253, 263, 299, 347; IR (neat) ν_{max} 3404, 3054, 1778, 1634, 1428, 896, 738 cm^{-1}; FABMS *m/z*: [M+H]+; EIMS *m/z* (rel int) 474 $[M]^+$, 352, 351, 338, 310, 309, 253, 136, 121, 115, 93, 77; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.96 (1H, m, H-3A), 3.02 (1H, m, H-3B), 4.66 (1H, dd, $J = 6.6$, 2.0 Hz, H-4), 4.19 (1H, m, H-10), 2.61 (1H, m, H-11), 7.18 (2H, overlap, H-16, 20), 7.28 (2H, overlap, H-17, 19), 7.26 (1H, overlap, H-18), 1.53 (3H, d, $J = 6.3$ Hz, H-21), 1.18 (1H, d, $J = 6.9$ Hz, H-22), 3.48 (2H, m, H-23), 1.83 (2H, m, H-25), 1.31 (1H, m, H-26), 1.80 (2H, s, H-28), 1.83 (3H, s, H-30), 0.85 (6H, s, H-31, 32), 12.4 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.4 (s, C-2), 36.5 (t, C-3), 34.1 (d, C-4), 105.1 (s, C-5), 157.5 (s, C-6), 108.2 (s, C-7), 159.2 (s, C-8), 79.2 (d, C-10), 46.0 (d, C-11), 200.1 (s, C-12), 104.1 (s, C-13), 156.8 (s, C-14), 140.9 (s, C-15), 126.7 (d, C-16), 128.9 (d, C-17), 127.3 (d, C-18), 128.9 (d, C-19), 126.7 (d, C-20), 19.6 (q, C-21), 10.1 (q, C-22), 25.5 (t, C-23), 125.9 (d, C-24), 25.9 (t, C-25), 35.9 (d, C-26), 29.2 (s, C-27), 46.6 (t, C-28), 125.4 (s, C-29), 19.7 (q, C-30), 28.0 (q, C-31, 32).
10. Inocalocyclide D (**4**): $[\alpha]_D^{25}$ −15.4° (*c* 1.0, CH_2Cl_2); IR (neat) ν_{max} 1776, 1685, 1606, 1456, 1374 cm^{-1}; EIMS *m/z* (rel int) 482 $[M]^+$, 440, 331, 318, 317, 275, 233, 219, 217, 177, 123, 109, 84, 69; ^1H NMR ($CDCl_3$, 300 MHz): δ 2,62 (1H, m, H-3A), 2.80 (1H, m, H-3B), 3.10 (1H, m, H-4), 4.20 (1H, m, H-10), 2.48 (1H, m, H-11), 1.45 (2H, m, H-15, 16), 0.88 (t, $J = 7.0$ Hz, H-17), 1.50 (3H, d, $J = 6.0$ Hz, H-21), 1.15 (1H, d, $J = 6.7$ Hz, H-22), 2.75 (2H, m, H-23), 2.39 (1H, m, H-24), 2.10 (2H, t, $J = 6.5$ Hz, H-25), 5.06 (1H, dd, $J = 6.6$, 6.5 Hz, H-26), 4.44 (1H, s, H-28A), 4.60 (1H, s, H-28B), 1.72 (3H, s, H-30), 1.56 (3H, s, H-31), 1.66 (3H, s, H-32), 2.39 (3H, s, OAc); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.8 (s, C-2), 33.9 (t, C-3), 29.4 (d, C-4), 114.2 (s, C-5), 159.6 (s, C-6), 116.3 (s, C-7), 159.8 (s, C-8), 78.9 (d, C-10), 47.1 (d, C-11), 192.7 (s, C-12), 109.4 (s, 13), 154.3 (d, C-14), 36.2 (t, C-15), 19.7 (d, C-16), 13.8 (q, C-17), 19.7 (q, C-21), 10.2 (q, C-22), 27.2 (t, C-23), 47.5 (d, C-24), 31.5 (t, C-25), 123.0 (d, C-26), 132.0 (s, C-27), 111.3 (t, C-28), 147.5 (s, C-29), 18.7 (q, C-30), 17.9 (q, C-31), 25.8 (q, C-32), 21.1 (q, $OCOCH_3$), 169.3 (s, $OCOCH_3$).