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Structural requirements for *ipso*-nitration with cerium(IV) ammonium nitrate (CAN)

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Abstract—Compounds in which the carbon skeleton contains at least a diarylmethane with the aromatic rings appropriately substituted by electron donating groups exhibited *ipso*-nitration when treated with cerium(IV) ammonium nitrate (CAN).

Potent cytotoxicity is exhibited by several lignan structure classes and their derivatives. Podophyllotoxin **1**, steganacin **2**, and burseran **3** are spindle poisons (Fig. 1).[1,2] We have attempted opening the B-ring of tetrahydrofurans (Fig. 2) to produce a burseran structural analog, which later could be closed to a steganicin counterpart. The first of these two steps has been explored using CAN in acetic acid and is described below.

Oxidation of benzylic carbon and nitration at aromatic carbon by the one-electron oxidant CAN has been conducted in various solvents.[3,4] We find CAN in acetic acid/water (9:1) converts tetrahydrofurans **4** and **5** through simultaneous *ipso*-nitration and oxidation to their respective dinitroburseran counterparts, **6** (32%) and **7** (28%), each isolated as a single diastereomer of undetermined configuration at the acetate center. When compound **5** was treated with CAN in neat acetic acid the yield of **7** rose to 41% while **4** under the same conditions gave the mononitroburseran type lignan **8** (39%) favoring one of two diastereomeric acetates (85:15). Products **6**–**8** were identified by HRMS, ^{1}H NMR, DEPT, COSY, HETCOR, and HMBC. Compounds **4** and **5** were oxidized also by cerium pyridinium, dimethylpyrazolium, and dimethylaminopyridinium nitrates in neat acetic acid. In each case the mononitroburseran type lignans were obtained. *ipso*-Nitration of the 1,2,3,4-tetrahydronaphthalene (THN) lignan galbulin by fuming nitric acid has been observed.[5]

Prompted by the foregoing results, structural and electronic factors favoring carbon–carbon cleavage by *ipso*-nitration using CAN in neat acetic acid were examined in models (**9**–**11**, Fig. 3) lacking a fused tetrahydrofuran. The mode of B-ring cleavage and product formation paralleled that of the lignan derivatives. However, action of CAN in acetic acid (neat, or 10% water) on diphenylmethane, 4-benzylanisole,[6] bis-

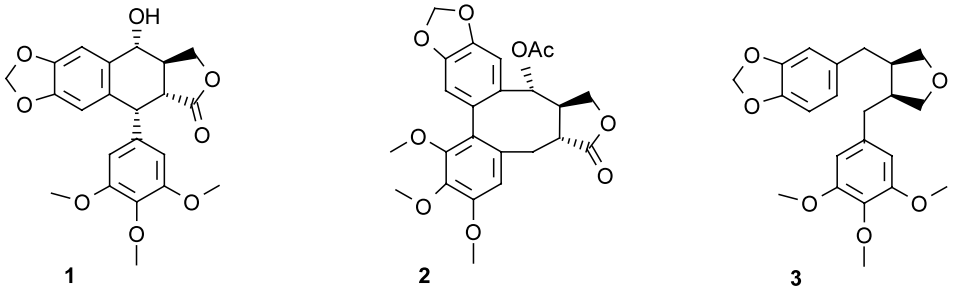

Figure 1. Structures of podophyllotoxin (**1**), steganacin (**2**) and burseran (**3**).

Keywords: tetrahydrofuran lignans; cerium ammonium nitrate; *ipso*-nitration.
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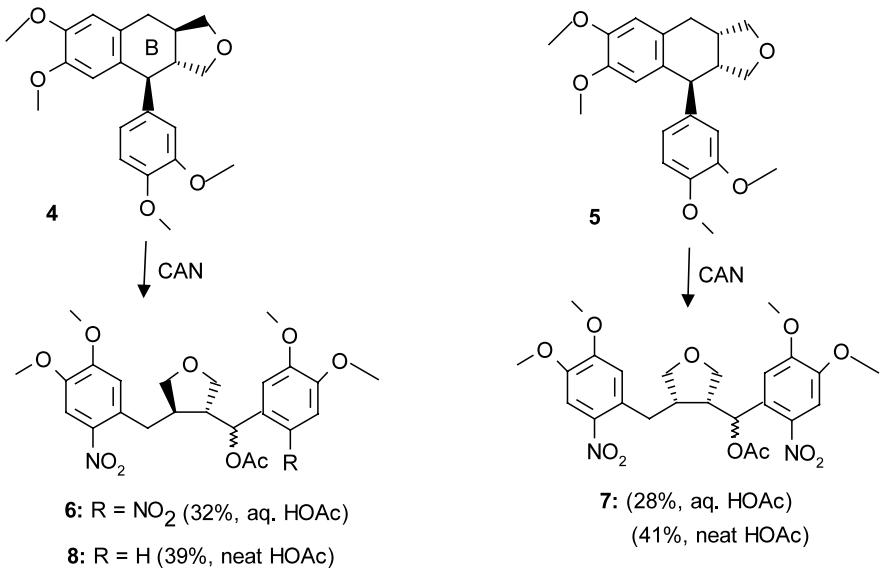

Figure 2. Oxidation of compounds **4** and **5** with CAN.

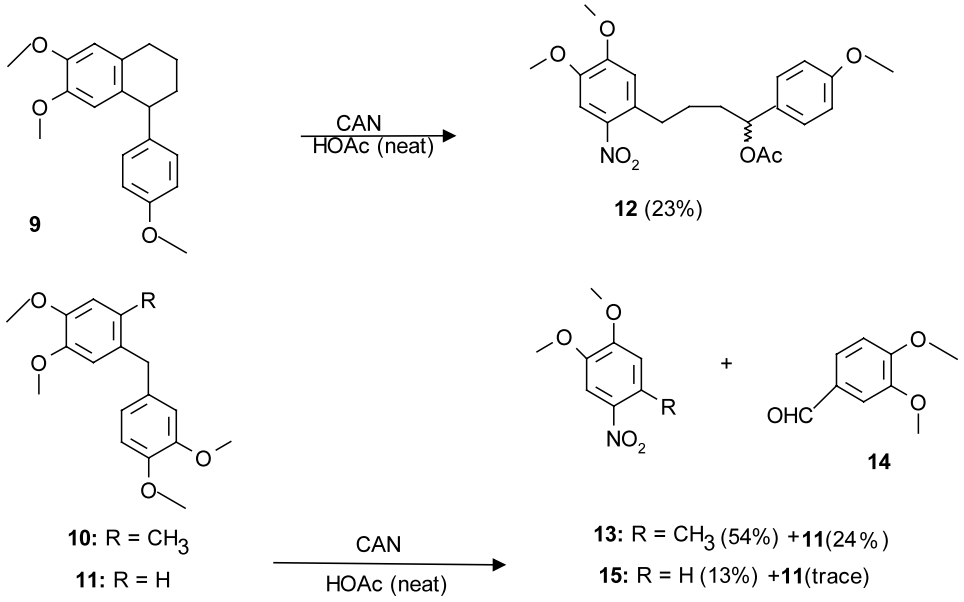

Figure 3. Oxidations of compounds **9**, **10** and **11** with CAN in neat HOAc.

(4-methoxyphenyl)methane,[7] 1-phenyl-1,2,3,4-THN,[8] and 6,7-dimethoxy-1-phenyl-1,2,3,4-THN[8] resulted in benzylic oxidation of methylene or methine carbon and gave ketones or alcohols without carbon–carbon bond cleavage. All these products were also known compounds and were identified by GC, ^{1}H and ^{13}C NMR and DEPT comparisons of the crude isolated products.[9] Identified products from treating the model 1-(3,4-dimethoxyphenyl)-THN with CAN in neat acetic acid were 1-(2-nitro-3,4-dimethoxyphenyl)-THN (43%) and an unstable 3-methoxy-5-(1-tetrahydronaphthyl)-1,2-benzoquinone (3.5%) resulting from oxidation of the pendant aryl group attached to the starting THN. The starting THN was recovered in 15% and a highly polar component mixture amounting to 32% of the crude product was obtained. No evidence for oxidative cleavage of the THN ring was obtained.

These results demonstrate that a diarylmethane is the minimal structural requirement for *ipso*-nitration if both aromatic rings are appropriately substituted by the electron donating methoxy groups such that the nitration is succeeded by nucleophilic attack at an electronically stabilized carbocation. The results are pertinent to the selection of lignan tetrahydrofurans for conversion to other structural types.

In a typical experiment, the organic reactant and CAN in a 1:4 ratio were mixed with the appropriate volume of solvent. The mixture was stirred for the required time for reaction at a given temperature. On workup, water was added and the resulting mixture was extracted with an organic solvent. The organic layer was washed with aqueous $NaHCO_3$. After evaporation of the organic solvent, the crude product was either

analyzed by GC MS or purified by chromatography for analysis by spectroscopic methods.

Acknowledgements

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9. Spectral and analytical data. Selected spectral data for **6**: $[\alpha]_D^{25}$ −181 (*c* 2.3, acetone); IR 3018, 1741, 1334, 867 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.43 (1H, s), 7.38 (1H, s), 6.53 (1H, s), 6.55 (1H, s, H-8), 6.36 (1H, d, $J=8.02$ Hz, H-4), 4.02 (1H, dd, $J=8.79$, 6.66 Hz, H-1), 3.93–3.99 (1H, m, H-3), 3.93 (3H, s, -OCH_3), 3.91 (3H, s, -OCH_3), 3.90 (3H, s, -OCH_3), 3.83 (1H, dd, $J=10.28$, 4.63 Hz, H-3), 3.80 (3H, s, -OCH_3), 3.61 (1H, dd, $J=8.86$, 5.01 Hz, H-1), 3.04 (1H, dd, $J=13.33$, 8.47 Hz, H-9), 2.95 (1H, dd, $J=13.34$, 6.16 Hz, H-9), 2.51–2.60 (2H, m, H-3a, H-9a), 1.99 (3H, s, $OCOCH_3$); ^{13}C NMR ($CDCl_3$) δ 20.7 (CH_3 of acetoxy), 36.7 (C-9), 41.3 (C-9a), 49.2 (C-3a), 56.0 (-OCH_3), 56.1 (-OCH_3), 56.2 (-OCH_3), 56.3 (-OCH_3), 70.1 (C-3), 70.7 (C-4), 73.7 (C-1), [107.5, 108.0, 108.1 (C-2′, C-5′, C-5)], 113.8 (C-8), [129.7, 129.8 (C-1′, C-8a)], [140.9, 141.0 (C-6′, C-4a)], [147.4, 148.2, 152.7, 153.1 (C-3′, C-4′, C-6, C-7)], 169.5 (C=O); HRMS [M^+] calcd for $C_{24}H_{28}N_2O_{11}$: 520.1693; found: 520.1732 (7.5 ppm deviation).
7: $[\alpha]_D^{25}$ −64.4 (*c* 2.2, acetone); IR 3013, 1743, 1519, 1330, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.65 (1H, s), 7.59 (1H, s), 6.96 (1H, s), 6.85 (1H, d, $J=3.75$ Hz, H-4), 6.77 (1H, s), 4.11 (1H, dd, $J=8.85$, 5.24 Hz, H-3), 3.97 (6H, s, -OCH_3), 3.92 (3H, s, -OCH_3), 3.92 (3H, s, -OCH_3), 3.85 (1H, t, $J=8.83$ Hz, H-3), 3.74 (1H, t, $J=7.61$ Hz, H-1), 3.68 (1H, t, $J=8.15$ Hz, H-1), 3.28 (1H, dd, $J=13.45$, 4.63 Hz, H-9), 3.08 (1H, dd, $J=13.48$, 10.57 Hz, H-9), 2.94–2.99 (1H, m, H-3a), 2.71–2.77 (1H, m, H-9a), 2.18 (3H, s, $OCOCH_3$); ^{13}C NMR ($CDCl_3$) δ 21.2 (CH_3 of acetoxy), 30.6 (C-9), 43.2 (C-9a), 45.4 (C-3a), 56.27 (-OCH_3), 56.37 (-OCH_3), 56.43 (-OCH_3), 56.46 (-OCH_3), 68.2 (C-3), 69.6 (C-4), 72.1 (C-1), [108. 51, 108.54, 113.4 (C-2′, C-5′, C-5, C-8)], [130.66, 130.70 (C-8a, C-1′)], [140.1, 141.1 (C-4a, C-6′)], [147.5, 148.4, 153.2, 153.6 (C-3′, C-4′, C-6, C-7)], 169.5 (C=O); HRMS [M^+] calcd for $C_{24}H_{26}N_2O_{11}$: 520.1693; found: 520.1716 (4.4 ppm deviation).
8: $[\alpha]_D^{25}$ −27.4 (*c* 11.5, acetone); ^1H NMR δ 7.41 (s, 1H, H-5), 6.44 (d, 1H, H-2′), 6.65–6.66 (overlapping peaks, H-5′, H-6′), 6.39 (s, 1H, H-2), 5.35 (d, 1H, H-7′), 4.00 (dd, $J=6.8$, 9.1 Hz, 1H, H-9′), 3.94 (s, 3H, OCH_3), 3.93 (1H, overlaps with OCH_3 peak, H-9), 3.92 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.75 (overlaps with OCH_3, 1H, H-9′), 3.58 (dd, $J=4.6$, 9.1 Hz, 1H, H-9), 3.06 (dd, $J=6$, 13.1 Hz, 1H, H-7), 2.66 (dd, $J=9.3$, 13.1 Hz, 1H, H-7), 2.34–2.4 (m, 2H, H-8, H-8′); ^{13}C NMR δ 21.2 (CH_3), 37.7 (C-7), 41.2 (C-8), 49.3 (C-8′), 56.0 (OCH_3), 56.1 (OCH_3), 56.2 (OCH_3), 56.3 (OCH_3), 70.7 (C-9′), 72.8 (C-9), 77.1 (C-7′), 107.9 (C-5), 108.3 (C-2′), 110.4 (C-5′), 114.2 (C-2), 119.2 (C-6′), 130.0 (C-1), 132.0 (C-1′), 140.0 (C-6), [147.2, 152.6, C-3, C-4], [148.5, 148.7, C-3′, C-4′], 169.9 (C=O); HRMS [M^+] calcd for $C_{24}H_{29}NO_9$: 475.1842; found: 475.18355 (−1.8 ppm deviation).
12: ^1H NMR δ 7.54 (s, 1H), 7.24 (dd, $J=2.21$, 6.8 Hz, 2H), 6.84 (dd, $J=2.12$, 6.66 Hz, 2H), 6.65 (s, 1H), 5.73 (t, $J=7.0$ Hz, 1H), 3.91 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 2.91 (t, $J=7.8$ Hz, 2H), 2.02 (s, 3H), 1.80–1.94 (m, 2H), 1.56–1.70 (m, 2H); ^{13}C NMR δ 21.1 (CH_3), 26.5 (CH_2), 33.1 (CH_2), 35.6 (CH_2), 55.0 (CH_3), 56.1 (CH_3), 75.1 (CH), 108.2 (CH), 113.1 (CH), 113.7 (CH), 127.8 (CH), 130.1 (CH), 132.2 (C), 132.4 (C), 140.9 (C), 147.1 (C), 152.9 (C), 170.2 (C=O)); HRMS [M^+] calcd for $C_{21}H_{25}NO_7$: 403.1631; found: 403.1637 (1.4 ppm deviation).