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A USEFUL SYNTHON FOR ELABORATION INTO IRIDOIDS AND ALKALOIDS[1]

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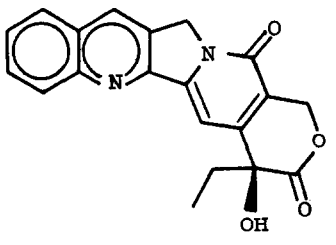
We are developing a general biomimetic synthesis of camptothecin (1), its analogs[2], and other medicinally important indole alkaloids, in which a key synthon is secologanin (2a) or a structurally similar compound. Although 2a is an abundant, easily isolable compound[3], its versatility as a synthetic intermediate is somewhat limited due to the difficulty in removing its glucosyl substituent in good yield and without extensive rearrangement of the aglucone[4]. Thus, we have developed an efficient synthesis of 2b[5] and of a synthon (7) that should be capable of elaboration to 3,4-dihydroanalogs of 2b, to 1, and to other indole alkaloids along already established lines[2,6]. Since this synthon appears to be generally useful, we are reporting its synthesis herein.



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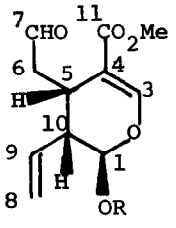


2a, R = D-glucose

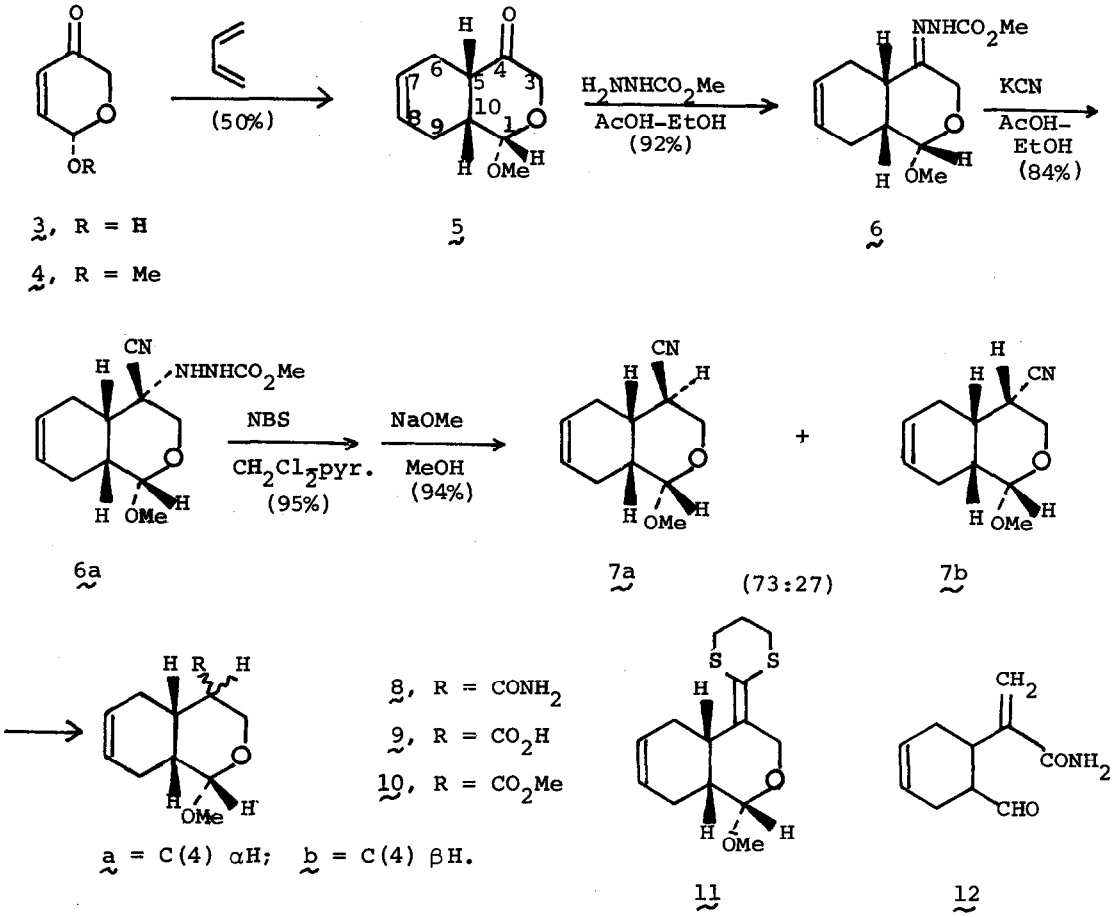
2b, R = Me

Our approach involves a Diels-Alder reaction of 2-methoxy-5-oxo-5,6-dihydro-2H-pyran (4) with butadiene followed by a one-carbon homologation to a C(11) nitrile. The latter then can be converted into an amide, acid, or methyl ester (Scheme).

The synthesis of 5 initially was attempted according to Jones[7]; contrary to his report, treatment of the Diels-Alder adduct of 3[8] under a variety of acetalization conditions gave a mixture of 5 and its C(4) ketal, the latter usually predominating. Consequently, we prepared 4 according to Torii et al.[9], from which 5 (m.p. 75°C) could be prepared directly in moderate yield[10] using the conditions reported by Jones[7] (excess butadiene, DME, 90-110°C). In this manner only one C(1) epimer of 5 was obtained, in contradistinction to the ca. 1:1 mixture of C(1) epimers obtained by the method of Jones[7].

The one-carbon homologation of 5 was attempted by several methods before a suitable route was found. Conversion of 5 to its ketenedithioacetal (11) by reaction with 2-lithio-2-trimethylsilyl-1,3-dithiane[11] proceeded well (85% yield), but subsequent hydrolysis[11] to the C(11) carboxyl or carbomethoxyl group could not be achieved in good yield. We attribute this difficulty

Scheme



to the acid sensitive acetal and nucleophilic nature of the C(7) double bond of 11. Similarly, the use of tosylmethylisocyanide, an established reagent for one-carbon homologation of aldehydes and ketones[12], was unsuccessful for preparation of 7. However, the desired homologation was smoothly achieved in 70% overall yield by the method of Ziegler and Wender[13] via the carbomethoxyhydrazone (6): 6 - m.p. 170-171°C; ir (KBr), ν, 3180, 3120, 2998, 2876, 1715 and 1680 cm^{-1}; ^1H NMR ($CDCl_3$), δ, 1.80-2.90 (m, 6H), 3.43 (s, 3H), 3.80 (s, 3H), 4.27 (AB q, J = 15 Hz, CCH_2O), 4.62 (d, J = 2Hz, $CHCH\langle^{O}_{O}$), 5.70 (br s, CH = CH), and 7.83 (br s, NH) ppm. 6a: m.p. 44.5-46°C; ^1H NMR ($CDCl_3$), δ, 1.80-2.60 (m, 6H), 3.38 (s, 3H), 3.79 (s, 3H, CO_2CH_3), 3.81 (s, 2H, CCH_2O), 4.29 (d, J = 4Hz, 1H), 4.60 (br s, J < 1Hz, 1H, NHN), 5.71 (br s, 2H), and 6.27 (d, J = 4Hz, 1H, $NNHCO_2$) ppm; ^{13}C NMR ($CDCl_3$), δ, 25.55 (d, C-5, C-10), 34.96, 36.55 (dt, C-6, C-9), 52.85 (q, C-1 OMe), 54.95(qCO_2Me), 62.67(d, C-3), 62.02(s, C-4), 98.84(d, C-1), 118.76(s, CN), 123.4, 125.6 (t, C-7, C-8), and 158.8 (s, C=O) ppm. 7a - m.p. 56.5-57.5°C; ir (KBr), ν, 3035, 2920, 2845, 2240, and 1660 cm^{-1}; ^1H NMR ($CDCl_3$), δ, 1.9-2.3 (m, 6H), 2.76 (br s, CHCN), 3.38 (s, 3H), 3.90, 3.92 (d AB q, J = 11, 12 Hz, $CHCH_2O$), 4.58 (br s, 1H), and 5.64 (br s, 2H) ppm; ms, m/e, 161.0837 (M^+-MeOH calcd 161.0847 for $C_{11}H_{15}NO_2$). 7b - m.p. 77-78.5°C; ir (KBr), ν, 3030, 2925, 2840 and 1660 cm^{-1}; ^1H NMR ($CDCl_3$), δ, 1.20-2.80 (m, 7H), 3.38 (s, 3H), 3.86, 3.89 (d AB q, J = 8, 11 Hz, 2H), 4.53 (d,

J = 3Hz, 1H), and 5.69 (br s, 2H) ppm; ms, m/e, 161.0836 (M^+-MeOH). The preferential formation of 7a is consistent with addition of HCN to 6a from the least hindered beta face followed by predominantly kinetic protonation of the C(4) carbanion during base catalysed decomposition of the cyanodiazene carboxylate[13]. TLC and ^{13}C NMR data failed to exhibit any evidence for the presence of two HCN adducts of 6, however.

The synthon represented by 7 was readily transformed into 8, 9, and 10 as follows: 8a - reflux 27 hr in aq. ethanol containing BioRad AG-1-X4 ($OH^\ominus$) ion exchange resin; 92%; m.p. 156-157°C; ir (KBr), ν, 3395, 3180, 3035, 2930, 2840 and 1660 cm^{-1}. 9a - reflux 8a 48 hr in 10N NaOH-EtOH (1:1); 85%; m.p. 160.5-163°C; ir (KBr), ν, 3450 br, 3025, 2910, 2840, 2650 br, and 1710 cm^{-1}. 10a - treatment of 9a with CH_2N_2 in CH_2Cl_2-MeOH; (60%); oil; ir ($CHCl_3$), ν, 1730 cm^{-1}; ^1H NMR ($CDCl_3$), δ, 1.4-2.6 (m, 7H), 3.34 (s, 3H), 3.66 (s, 3H, OCH_3) 3.72, 3.82 (d AB q, 2H), 4.48 (d, J = 5Hz, 1H) and 5.60 (br s, 2H). Direct hydrolysis of 7a to 9a under strongly basic conditions gave predominantly the ring opened compound 12 resulting from beta elimination, which is why a two-step reaction sequence was chosen. Thereby the formation of diene 12 was reduced to a minor amount. Attempted methanolysis of 7a to 10 using dry HCl gas and methanol gave apparent rearrangement products (20%) plus the C(1) hemiacetal of 7a (60%), although this method worked well for the conversion of cyclohexyl nitrile to 1-carbomethoxy cyclohexane.

The analogous derivatives of 7b were also obtained using identical reaction conditions: 8b - 78%, m.p. 153-156°C; ir (KBr), ν, 3390, 3175, 3020, 2910, 2835, and 1660 cm^{-1}. 9b - 72%; m.p. 68-71°C; ir (KBr), ν, 3400 br, 3020, 2910, 2850, 2650 br, and 1710 cm^{-1}. 10b - 70%; ir ($CHCl_3$), ν, 1730 cm^{-1}, ^1H NMR ($CDCl_3$), δ, 1.5-2.6 (m, 7H), 3.35 (s, 3H), 3.66 (s, 3H), 3.71 (d AB q, 2H), 382, 4.48 (d, J = 3Hz, 1H), and 5.60 (br s, 2H) ppm.

The utility of 9 for the synthesis of 1 is being explored, based on the methodology of van Tamelen[6b,c]. Using a similar approach it should be possible to employ 10 in the synthesis of geissoschizine[6b] and ajmalicine[6d].

References and Notes

1. This research was supported by the National Institutes of Health research grant CA 17127-03 and career development award to C. R. H. (CA-00253-01).
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