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A SYNTHETIC APPROACH TO SECOLOGANIN: SYNTHESIS OF A PROTECTED FORM OF THE SECOXYLOGANIN AGLUCONE

Peter T. W. Cheng and Stewart McLean*,
Department of Chemistry, University of Toronto, Toronto, M5S 1A1, Canada.

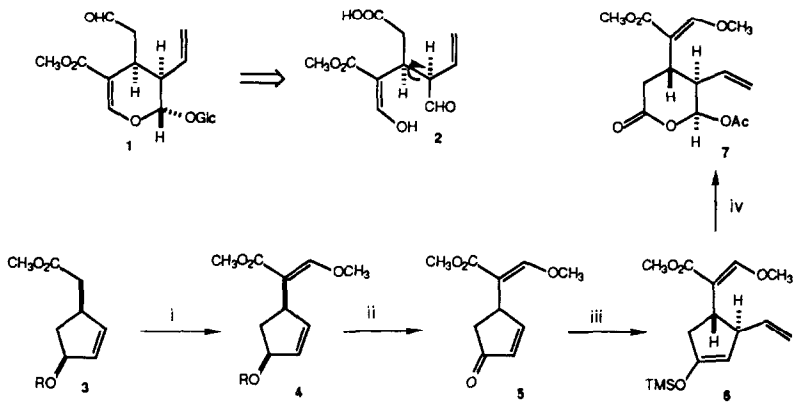
Abstract: A short synthesis of 7, a protected form of the secoxyloganin aglucone, is described. Key steps are conjugate addition to a cyclopentenone and oxidative cleavage of the silyl enol ether thus obtained.

Secologanin (1) is of central importance in the biosynthesis of a vast array of alkaloids[1]. Its dense aggregation of functional and stereochemical features makes it a challenging target for total synthesis. The instability of its aglucone further complicates synthetic planning. Total syntheses of protected forms of the aglucone[2,3] and of a rearranged aglucone[4] have been reported, but no total synthesis of secologanin itself has yet appeared. Our synthetic strategy set the aglucone of secoxyloganin, the carboxylic acid corresponding to aldehyde 1, as the first target. The aglucone is depicted in its acyclic form 2 in order to illustrate the retrosynthetic logic.

Hydroxy ester 3 (R=H) was conveniently prepared from racemic 5-norbornen-2-one[5] (which may also be obtained in either enantiomeric form), and protected as its ethoxyethyl (EE) ether[6]. Treatment of 3 (R=EE) with ethyl formate and two equivalents of lithium diisopropylamide provided the C-formylated derivative, which was immediately converted to the enol ether 4 (R=EE) by the action of methyl sulfate and potassium carbonate. The EE group was removed by treatment with pyridinium p-toluenesulfonate, and the resulting alcohol 4 (R=H) was oxidized to the cyclopentenone 5 by pyridinium dichromate. Reactions of 5 with a variety of cuprate reagents generally gave unsatisfactory results, but the following conditions were effective: 5 was treated with vinylmagnesium bromide (3 equivalents), a catalytic amount of cuprous iodide, chlorotrimethylsilane, and hexamethylphosphoramide in tetrahydrofuran for 10 h at -75°C, 4-dimethylaminopyridine was added, and the temperature was allowed to rise slowly to -40°C. Workup provided 6 in excellent yield; only one isomer could be detected (by gc of 6; gc and ^{13}C nmr spectrum of desilylated 6).

The oxidative cleavage of 6 was most successfully accomplished by treatment with 32% peracetic acid (2 equivalents) in dichloromethane at 0°C in the presence of anhydrous sodium acetate and sodium carbonate. Under these conditions, 6 was oxidized to the corresponding α-acetoxycyclopentanone, which then underwent a Baeyer-Villiger oxidation to provide 7 in 71% yield. The

stereochemistry of 7 is apparent from its ^1H nmr spectrum, which shows $J_{3,4}$ = 11.4 Hz and $J_{4,5}$ = 2.9 Hz. Thus, 7 is a protected form of 2, incorporating the ten-carbon skeleton, functionality at the correct oxidation level, and stereochemistry of the secoxyloganin aglucone. The present product is racemic, but the same diastereoselective route will obviously lead to either the natural or unnatural enantiomer depending on which enantiomer of 5-norbornen-2-one is chosen as starting material.



i. a) LDA (2 eq), HCO_2CH_3; b) Me_2SO_4, K_2CO_3, Me_2CO (Yield 72% 4(R = EE) + 7% 2 isomer - separated by flash chromatography)

ii. a) PPTS (1 eq), Me_2CO, 23°C; b) PDC, 4Å mol. sieves, EtOAc (Yield 60%)

iii. CH_2=CHMgBr (3 eq), CuI (cat), HMPA (3 eq), TMSCl, THF, -75°C, then DMAP, -75°C to -40°C (Yield 75 - 100%)

iv. CH_3CO_3H (2 eq), NaOAc, Na_2CO_3, CH_2Cl_2 (Yield 71%)

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6. Spectroscopic characteristics of all compounds were in accord with the structures assigned. All isolable new compounds were characterized by their nmr (^1H and ^{13}C) and high-resolution mass spectra.

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