Tetrahedron Letters No. 38, pp 3593 - 3596. 0040-4039/79/0915-3593$02.00/0

SYNTHESIS OF THE CARBON FRAMEWORK OF OLIVIN

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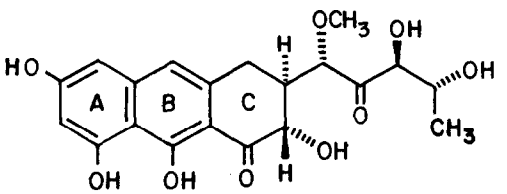
Summary: A convergent synthetic approach is outlined to the tricyclic compound 10, which contains the full carbon skeleton of olivin.

Olivin (1) is the aglycone of the olivomycin group of antitumor antibiotics.[2] These compounds, along with the structurally related chromomycins[3] and mithramycins,[4] are currently being evaluated in the clinic[5] as cancer chemotherapy agents. We recently described a synthetic approach to the tricyclic nucleus of olivin.[6] However, our synthesis was rather long, and thus



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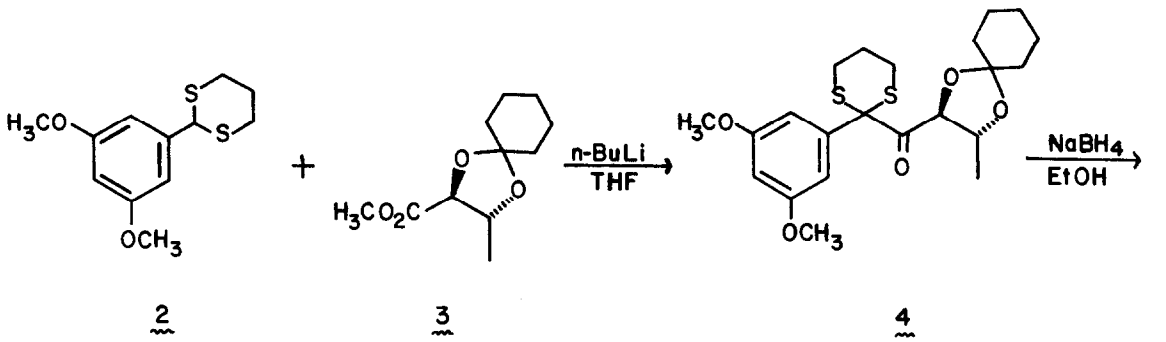
we have recently concentrated on developing a shorter, more convergent route to the olivin skeleton. In this note we describe an efficient synthesis of tricyclic compound 10 which contains the complete carbon framework and much of the functionality of olivin (1).

Our starting material was dithiolane 2, which was prepared in 77% yield from 3,5-dimethoxybenzaldehyde on treatment with 1,3-propanedithiol in $CHCl_3$ saturated with dry HCl[7] (mp 94-95°C). Acylation of the anion derived from 2 (n-butyl lithium, THF, -20°) with readily available ester 3[8] at -78° gave the ketone 4 (63% based on 2; IR (film) 1720 cm^{-1}). Sodium borohydride reduction of this ketone (EtOH, room temp, 24 hr) gave alcohol 5 (99%, as a 70:30 mixture of

diastereomers[9]). Further reduction of 5 with $Li/NH_3/EtOH$ afforded the dienol ether 6.[10] Without purification 6 was rapidly hydrolyzed (THF/5% HCl, 5 min, room temp) to the corres-



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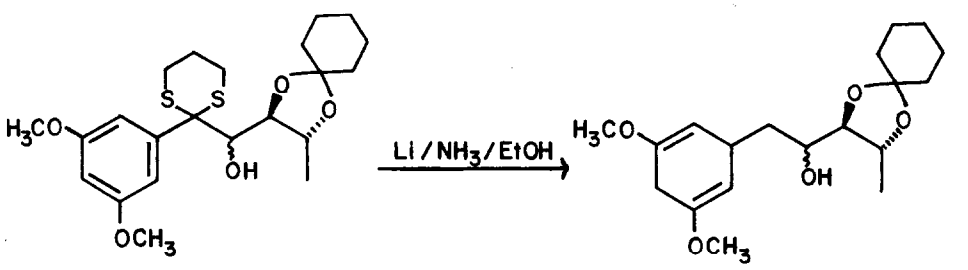

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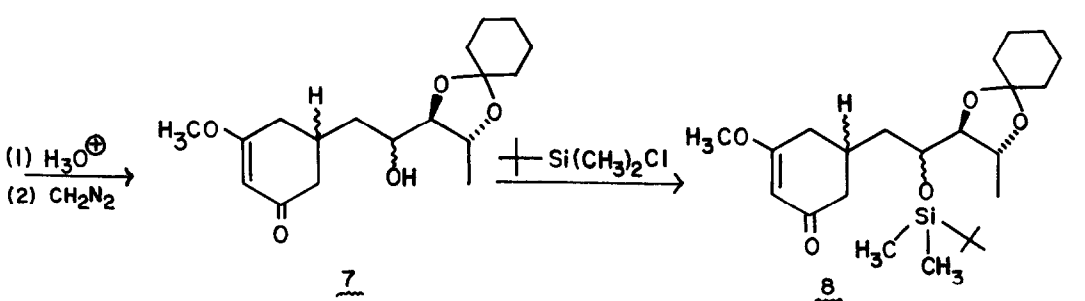

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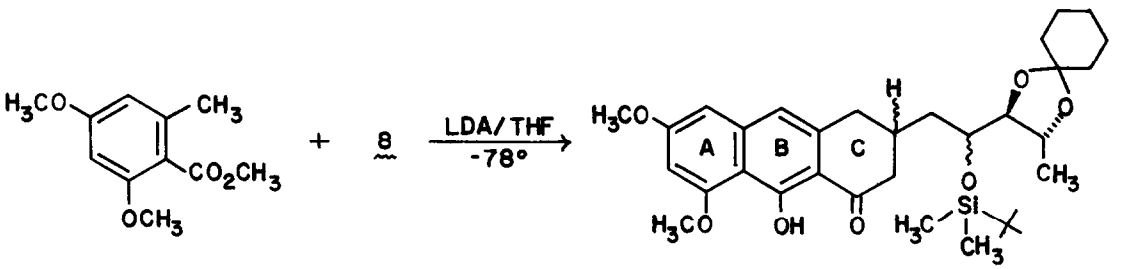
ponding 1,3-diketone which was immediately methylated[11] with ethereal diazomethane to afford β-methoxyenone 7 (34% overall yield from 5; NMR ($CDCl_3$) δ5.34 (1H, s), 3.70 (3H, s); IR (film) 1660 and 1620 cm^{-1}). The hydroxyl group of 7 was protected by silylation ($((CH_3)_2[C(CH_3)_3]SiCl$, DMF, imidazole, room temp[12]) to give 8 in 95% yield.

Construction of the tricyclic nucleus of olivin was effected by condensing the anion derived from orsellinate 9 (1.5 equiv LDA/THF, -78°) with β-methoxyenone 8 to afford tricyclic 10 in a single step in 40% yield as a mixture of diastereomers.[13] Such a strategy for synthesis of polycyclic aromatics appears to be quite general, and we intend to explore it further.[14]



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We are presently attempting to introduce the methoxyl and hydroxyl groups of olivin (1) into 10 stereoselectively using methodology previously developed in our model studies.[6] We are also trying to suitably modify the synthetic route to 8 in order to avoid stereochemical problems due to isomers at the C-ring assymmetric center. However, the above sequence of reactions is amenable to large scale preparation of 10.[15]

Acknowledgement. This work was generously supported by the National Cancer Institute (CA-25145) We thank Mr. A. Freyer for FT-NMR spectra and Dr. R. Minard for mass spectra.

References and Notes

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9. Since this center will eventually be destroyed, no attempt was made to develop a stereoselective reduction of the carbonyl group.
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15. Yields have not yet been optimized.

(Received in USA 7 June 1979)