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# FURANS AS INTERMEDIATES FOR THE SYNTHESIS OF OXYGENATED NATURAL PRODUCTS. ASYMMETRIC SYNTHESIS OF PRELOG-DJERASSI LACTONE.

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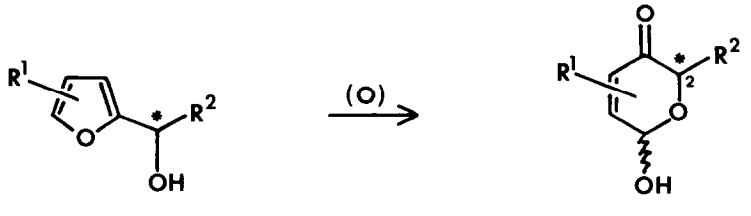
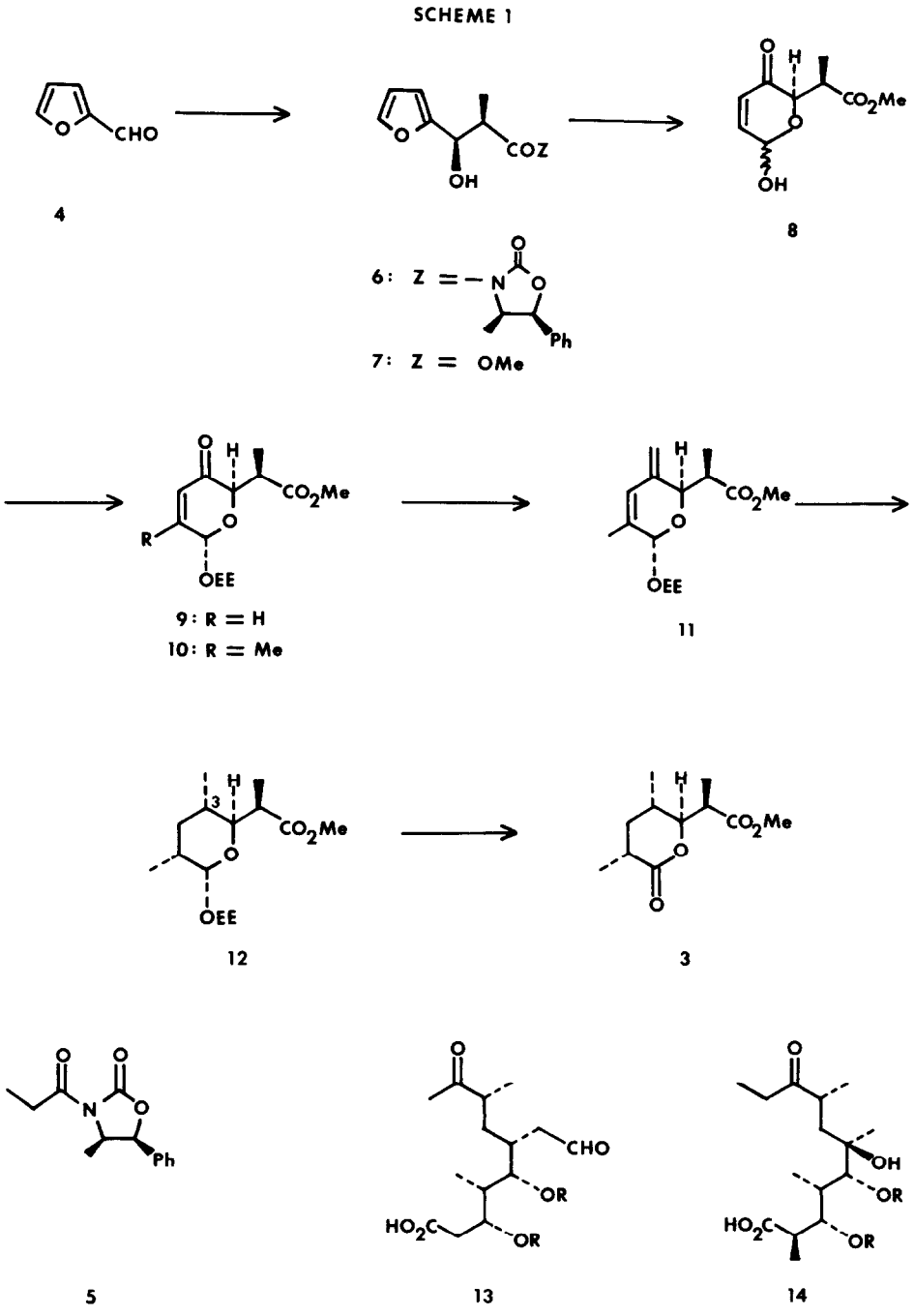
**Abstract.** A facile, asymmetric synthesis of the methyl ester of Prelog-Djerassi lactone (3) has been completed in nine steps from furfuraldehyde (4).

Some time ago we embarked upon a series of investigations directed toward the design and development of a general protocol for the asymmetric synthesis of oxygenated natural products by exploiting substituted furan derivatives as the key intermediates. The inspiration for this strategy was derived from the established precedent that furans may serve as latent 1,4-dicarbonyl compounds and that furfuryl alcohols may be smoothly converted into hydro-3-pyranones by oxidation (eqn. 1).[2] Derivatives of hydropyrans have proven to be important intermediates in the total syntheses of a wide variety of natural products, and in the present instance it is particularly significant that the hydropyranone 2 is generously endowed with differentiated functionality, which may be subsequently exploited for the facile introduction of other functional groups and alkyl residues. The stereochemical outcome of these transformations would then be subject to control by the substituents already present on the hydropyranone ring. Thus, if the carbinol 1 was available in optically pure form, the absolute chirality at C(2) of the derived hydropyranone 2 could be exploited for the




1 2 (1)

SCHEME 1


CHO
4
COZ
OH
6: Z = –N O Ph
7: Z = OMe
H
CO2Me
O
OH
8
R
OEE
9: R = H
10: R = Me
11
3
12
3
5
HO2C
OR
13
14

stereoselective elaboration of other stereocenters in the targeted natural products. We have recently applied this strategy to a concise, asymmetric synthesis of tirandamycic acid,[3] and we now wish to record the successful application of this novel methodology to the asymmetric synthesis of the methyl ester of Prelog-Djerassi lactone (3),[4] which constitutes the C(1)-C(7) fragment of the macrolide antibiotic methymycin.

In the event, furfuraldehyde (4) was allowed to react with the boron enolate derived from the chiral imide 5 according to the elegant method of Evans[5] to provide the aldol adduct 6 with >99% diastereoselectivity.[6] Methanolysis (sat'd $K_2CO_3$/MeOH, 0 °C, 2 h) of 6 provided the enantiomerically pure methyl ester 7 in about 75% overall yield from 4. Oxidation [1M $Br_2$-$CHCl_3$ (2 equiv), MeOH, -78 °C, 30 min] of 7 followed by acid-catalyzed hydrolysis [10% aq $H_2SO_4$-THF (1:1), RT, 24 h] of the intermediate 2,5-dihydro-2,5-dimethoxyfurans afforded the hydropyranones 8 (88%) as a mixture of α- and β-anomers. Protection of the anomeric hydroxyl group was readily achieved by treatment of the hydropyranones 8 with excess ethyl vinyl ether in the presence of a catalytic amount of pyridinium p-toluenesulfonate at room temperature, to provide a mixture (α:β = 4:1) of anomers from which the desired α-anomer 9 could be separated by conventional HPLC in 58% yield.[7] Transformation of 9 into the homolog 10 was smoothly effected in 63% overall yield by sequential treatment with lithium dimethylcuprate (1.1 equiv, $Et_2O$, -78 → -30 °C, 1 h) and chlorotrimethylsilane (1.05 equiv) followed by oxidation of the intermediate silyl enol ether with palladium acetate[8] (4 equiv, $CH_3CN$, RT, 94 h). Wittig methylenation [$Ph_3P{=}CH_2$ (4.0 equiv), THF, -78 → 0 °C, 1 h) of 10 proceeded smoothly to afford 11 in 81% yield. Catalytic hydrogenation [$H_2$ (1 atm), 10% Pd-C, EtOAc, RT, 48 h] of the diene 11 proceeded with a high degree of stereoselectivity to provide 12 as the major product (72% yield) together with a minor product (< 8%), which has been tentatively identified as being epimeric at C(3). Although a wide variety of other conditions (catalyst, solvent, pressure, etc.) for effecting the catalytic reduction of the diene 11 were examined, none proceeded with a higher degree of stereoselectivity. Completion of the synthesis by treatment of the lactals 12 with excess Jones reagent ($H_2CrO_4$, aq $Me_2CO$, RT, 2 h; 76%) afforded the methyl ester of Prelog-Djerassi lactone (3).[9]

The efficacy of exploiting 10 as a key intermediate for the syntheses of 13 and 14, which encompass C(1)-C10) of tylonolide and erythronolide, respectively, is being investigated as

are other applications of this strategy for the asymmetric synthesis of oxygenated natural products. The results of these investigations will be reported in due course.

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6. The structure assigned to each compound was in accord with its spectral ($^{1}H$ and $^{13}C$ NMR, IR, mass) characteristics. Analytical samples of all new compounds were obtained by preparative HPLC and gave satisfactory combustion analysis (C, H) and/or identification by high resolution mass spectrometry. All yields are based upon isolated materials after purification by chromatography or recrystallization.

7. Since the ethoxyethyl protecting group possesses a stereocenter, compounds 9 - 12 were obtained as mixtures of epimers, which could be separated by preparative HPLC and individually characterized, but reactions were generally performed on the epimeric mixtures.

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9. The Prelog-Djerassi lactonic acid methyl ester 3 thus obtained was identical in all respects with that of a sample prepared independently by Ireland and Daub.[4a]

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