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ACYCLIC STEREOCONTROL VIA THE CLAISEN REARRANGEMENT: A FORMAL SYNTHESIS OF (+) TIRANDAMYCIC ACID

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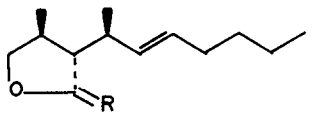
Abstract: The optically active lactone 1a, prepared previously by the Claisen rearrangement, serves as a starting material for the synthesis of (-) alcohol 7b which has been utilized by Ireland in the synthesis of tirandamycic acid 8a.

The unique bicyclic ring system of tirandamycin (8b),[1] an acyltetramic acid antibiotic, has inspired several synthetic efforts directed towards its total synthesis. Tirandamycic acid (8a), a degradation product of tirandamycin, has been synthesized by Ireland in optically active form from D-glucose.[2] We have reported[3] the applicability of furan chemistry to the construction of models for the bicyclic portion of tirandamycic acid. Subsequently, DeShong reported[4] similar studies and, more recently, has employed the furan approach, in conjunction with tested aldol methodology, in a synthesis of the racemate of Ireland's alcohol 7b.[5] This Letter details a Claisen rearrangement-based methodology for acyclic diastereoselection which employs the furan approach in the synthesis of Ireland's chiral intermediate 7b.

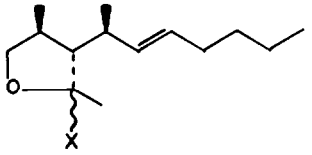
Lactone 1a, both diastereomerically and enantiomerically pure, is produced through the Claisen rearrangement of S-3-methylbutyrolactone (as its diethoxy ortholactone) and R-(E)-2-octen-4-ol.[6] Exposure of lactone 1a to Tebbe's reagent[7] ($Cp_2TiCH_2ClAlMe_2$, 1.1 equiv; toluene/THF/pyridine; 45 min -55°C, → 25°C, 3h) provided the crude enol ether 1b (δ 3.84 and 4.32 (2x1H, br. s, $=CH_2$)), which was immediately transformed into the hydroperoxides 2a (30% H_2O_2, THF/HOAc, -10°C, 72 h) in 82% overall yield.[8] Criegee rearrangement of the hydroperoxides[9] (Ac_2O/Et_3N/DMAP; CH_2Cl_2; 0° → 25°; 30 min) via acylperoxides 2b afforded a mixture of hydroxy acetates which was directly saponified (K_2CO_3, aq. MeOH, 2.5 h) to provide diol 3 in 86% yield.

Transformation of the diol into its acetonide ($Me_2C(OMe)_2$, p-TsOH, 25°C, 98%) followed by ozonolysis (CH_2Cl_2, -78°C, DMS) gave rise to chiral aldehyde 4a, previously prepared by Kishi from S-3-hydroxy-2-methylpropionic acid.[10,11]

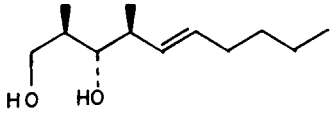
Lithiation of 2,3-dimethylfuran (nBuLi; THF/hexane, -20°C, 4h) followed by the addition (THF; -78°C, 1h; 25°C, 1h) of aldehyde 4a to the organometallic, provided the syn alcohol 5a (58%) and the anti alcohol 5b (34%) after silica gel chromatography.[12] The major furfuryl alcohol was oxidized (m-ClpBA, 1.1 equiv, CH_2Cl_2, 0°C, 30 min) to a mixture of anomeric dihydropyranones 6a. Hydrolysis of the acetonide group of 6a led to none of the desired bicyclic 7b.[13]



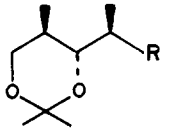
1a, R = O
b, R = CH_2



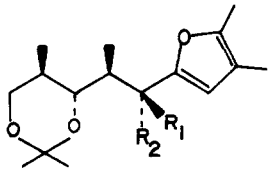
2a, X = OOH
b, X = OOAc



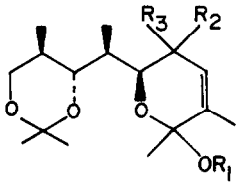
3



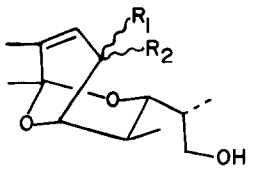
4a, R = CHO
b, R = CH_2OH



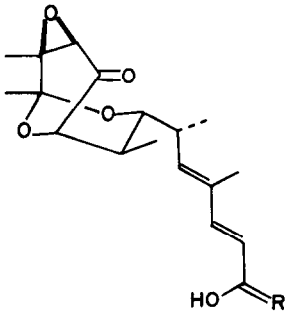
5a, R_1 = OH, R_2 = H
b, R_1 = H, R_2 = OH



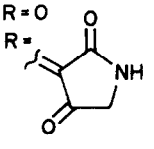
6a, R_1 = H, R_2,R_3 = O
b, R_1 = CH_3, R_2,R_3 = O
c, R_1 = CH_3, R_2,R_3 = H, OH



7a, R_1,R_2 = H, OH
b, R_1,R_2 = O



8a, R = O
b, R =



This difficulty was circumvented in the following manner. Protection of the dihydropyranones 6a as a methoxyketal (MeOH, pyridinium p-toluenesulfonate (PPTS), 25°C, 30 min) gave a single, crystalline stereoisomer 6b (65% yield from 5a, based upon recovered 6a). Reduction of 6b ($NaBH_4$, $CeCl_3$, MeOH, 0°C, 20 min) gave rise to a mixture of epimeric alcohols 6c which, upon exposure to acid, (MeOH, PPTS, 25°C, 15h) afforded the desired mode of cyclization providing a mixture of alcohols 7a. Oxidation (MnO_2, $CHCl_3$, 25°C, 36 h) of the allylic alcohol mixture provided Ireland's alcohol in 51% yield from 6b (60% based upon recovered 7a) whose spectroscopic properties were identical with reported data.[11]

Attempts to cyclize the anti-allylic alcohol diastereomer of 6c (derived from 5b) gave rise to several inseparable and unidentifiable products.

The study provides an initial application of the Claisen rearrangement in the control of acyclic diastereoselection which complements current methodology in this area.

ACKNOWLEDGMENTS: Support for this work was provided by NIH grant AI-15617. The award of a Dox Fellowship (1982-83) to RTW is greatly appreciated. Initial studies in this area were conducted by Dr. John Thottathil. We are indebted to Professors Kishi (Harvard) and Ireland (Cal Tech) for spectral data relating to 4a and 7b, respectively. High field NMR spectra were recorded at the Northeast Regional NSF/NMR Facility, Department of Chemistry, Yale University, supported by grant CHE-7916210 from the Chemistry Division of the National Science Foundation.

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8. These reaction conditions are critical. Stronger acid effects isomerization of the - substituent.
9. S.L. Schreiber and W.-F. Liew, Tetrahedron Lett., 2363 (1983).
10. a) H. Nagaoka, W. Rutsch, G. Schmid, H. Iio, M.R. Johnson, and Y. Kishi, J. Am. Chem. Soc., 102, 7962 (1980); b) M.D. Lewis and Y. Kishi, Tetrahedron Lett., 2343 (1982).
11. All new compounds gave correct spectral and compositional data. NMR and rotation data confirmed the structures of 4b ($LiAlH_4$ reduction of 4a) and 7b. 4a: NMR (270 MHz, $CDCl_3$): δ 0.78 (d, J = 6.6 Hz, 3H), 1.20 (d, J = 7.1 Hz, 3H), 1.37 (s, 3H), 1.43 (s, 3H), 1.94 (m, 1H), 2.52 (m, 1H), 3.50 (t, J = 11 Hz, 1H), 3.71 (m, 2H), 9.78 (d, J = 2.5 Hz, 1H); 4b:

$[\alpha]_D^{25}$ = -23.24° ($CHCl_3$: c = 2.30); lit[10] $[\alpha]_D$ = -22.8° NMR (270 MHz, $CDCl_3$): δ 0.76 (d, J = 6.6 Hz, 3H), 1.13 (d, J = 7.3 Hz, 3H), 1.40 (s, 3H), 1.42 (s, 3H), 1.83-2.02 (m, 2H), 2.77 (dd, J = 1.6, 8.6 Hz, 1H), 3.51 (m, 3H), 3.74 (dd, J = 5.1, 11.6 Hz, 1H), 3.96 (br. d, J = 10.9 Hz, 1H); 7b: $[\alpha]_D^{25}$ = -300.4° ($CHCl_3$: c = 0.245); lit[2] $[\alpha]_D^{RT}$ = -310.2° NMR (500 MHz, $CDCl_3$): δ 0.78 (d, J = 7.1 Hz, 3H), 1.10 (d, J = 7.2 Hz, 3H), 1.55 (s, 3H), 1.90 (m, 1H), 1.93 (d, J = 1.5 Hz, 3H), 2.05 (dd, J = 2.6, 8.7 Hz, 1H), 2.41 (m, 1H), 3.52 (dd, J = 2.1, 11.4 Hz, 1H), 3.63 (m, 1H), 3.93 (dt, J = 3.0, 11.2 Hz, 1H), 4.11 (d, J = 6.0 Hz, 1H), 6.15 (s, 1H); mp. 58-59°C (ether-pentane, -20°C).

12. An excess of the syn-diastereomer was anticipated with aldehyde 4a.[10b] In the DeShong study,[4] an ~ 1:1 mixture of syn:anti alcohols was obtained.
13. It appears that the primary hydroxyl group requires protection. In some of our related studies, rearrangement products have been identified.

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