A CHIRAL, NON-RACEMIC C_1-C_7 ERYTHRONOLIDE SYNTHON USING THE 3-METHYL-γ-BUTYROLACTONE STRATEGY[1]

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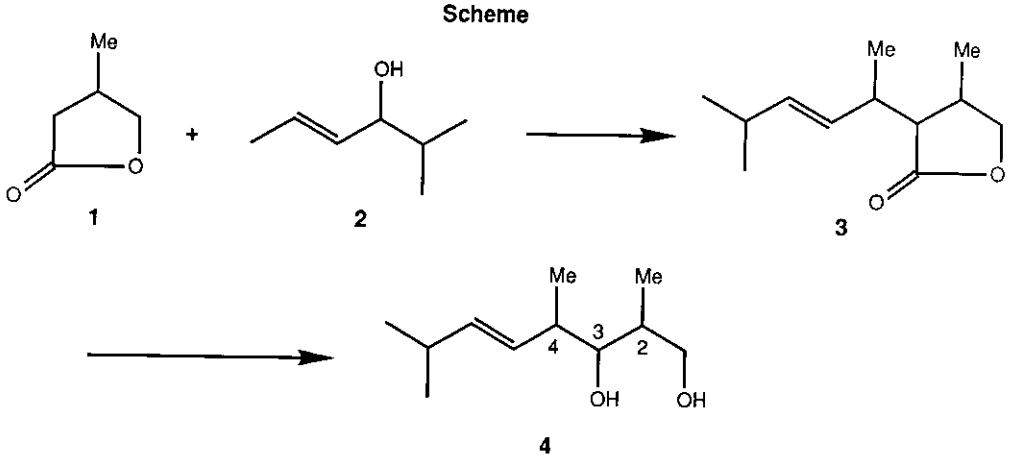
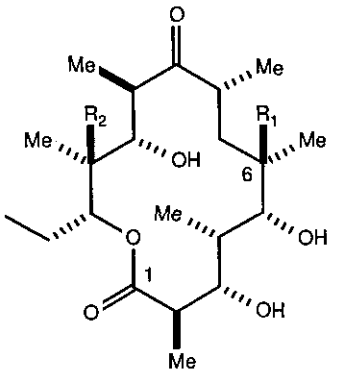
Abstract —— A chiral, non-racemic C_1-C_7 unit for the synthesis of the erythronolides has been prepared. R-3-Methyl-γ-butyrolactone serves as the template for the synthesis. The stereochemistry at C_3 of the synthon 13 was established by stereoselective, kinetic protonation of the enolates of lactones 9 and 10.

We have developed two procedures using R or S lactone 1 and R or S alcohol 2 that provide three of the four possible diastereomers (six enantiomers) of lactone 3.[2] Since the stereoisomeric lactones 3 (Scheme) can be induced to undergo oxidative decarboxylation with retention of configuration, they can be transformed into their respective diols 4. Only the 2,3-syn, 3,4-syn diastereomer of diol 4, and its congener 3, cannot be realized directly by our methodology. The ability to realize syn-syn stereochemistry is important as it appears at C_3-C_5 in erythronolide A (5a) and 6-deoxyerythronolide B (5b).[3] In this communication we reveal a solution to this problem.

Scheme





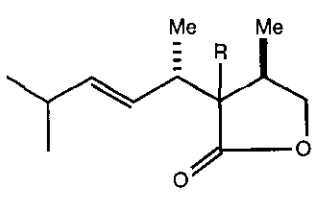
5a, $R_1 = R_2 = OH$

b, $R_1 = R_2 = H$

R-3-Methyl-γ-butyrolactone diethylortholactone (%ee=97.4) and R-2-methyl-4(E)-hexen-2-ol 2 (%ee>99%) were subjected to Claisen rearrangement (toluene, reflux; pivalic acid, cat.; 48h) affording epimeric lactones 6a/6b (54/46) whose equilibration (t-BuOK, t-BuOH-Et_2O, 25°C, 18h) gave a 98/2 mixture of 6a/6b in 94% overall yield. Formal Baeyer-Villiger oxidation of lactone 6a was accomplished via the Criegee rearrangement sequence (*MeLi*, Et_2O, 0°C; *aq.* H_2O_2, *HOAc*, *THF*; Ac_2O, Et_3N, DMAP, CH_2Cl_2, then heat at 40°C; $LiAlH_4$; $Me_2C(OMe)_2$, p-TsOH),[2b,c] providing the acetonide 7 in 82% yield for the five steps. Iterative homologation of lactone 6a to lactone 8a was completed as follows. Ozonolysis of olefinic acetonide 7 (O_3, MeOH; $LiAlH_4$, Et_2O), chain extension (*TsCl*, *pyr.*, 25°C, 18h; *NaCN*, *DMSO*, 90°C, 4.5h), hydrolysis (HCl, H_2O/MeOH, reflux, 18h), and silylation (t-$BuPh_2SiCl$, imidazole, DMF, 25°C, 18h) afforded lactone 8a in 63% yield from acetonide 7.

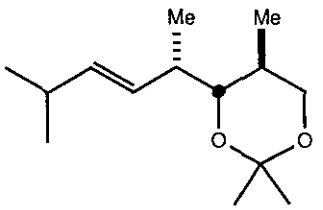
Carbomethoxylation of lactone 8a (2 equiv. LDA, THF/HMPA, –78°C, then $NCCO_2Me$, 1h; 98% yield) set the stage for further chain extension. Alkylation of the sodium salt of lactonic ester 8b (NaH, THF) with the diethyl phosphate ester of R-2-methyl-4(E)-hexen-2-ol 2 (5 mol % $(Ph_3P)_4Pd$, 5 mol % Ph_3P, THF, 0°C, 45 min, 25°C, 1h) followed by Krapcho decarboxylation (LiCl, DMSO/H_2O, 190°C, 4h) gave 2,3-cis lactone 9 (73%, mp 115-116°C) and 2,3-trans-lactone 10 (21%, mp 67-69°C).

The 2,3-cis stereochemistry of lactone 9 was confirmed when it was transformed via the Criegee sequence[4] into acetonide 11 (87%). The nmr spectrum of acetonide 11, which can have the



6a, R = β -H

b, R = α -H



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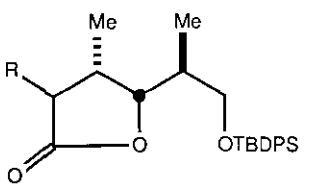
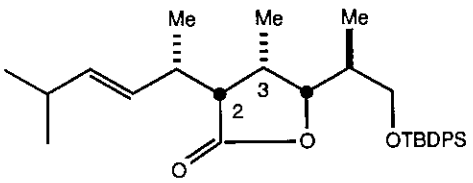


8a, R = H

b, R = CO_2Me



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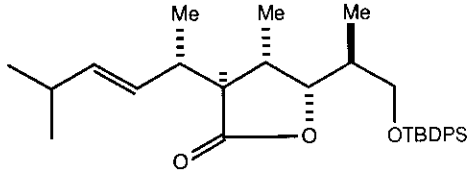

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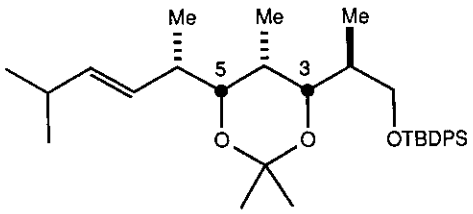

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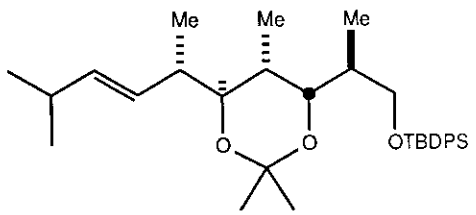

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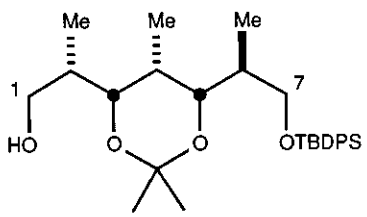

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1,3-dioxane ring exist in a chair, revealed the C_3-methine proton at δ3.82 (dd, J=10.0, 1.9 Hz) and its C_5 counterpart at δ3.45 (dd, J=9.9, 1.9 Hz); the smaller couplings arise from the C_4-methine proton. The C_3-proton of acetonide 12, derived from 2,3-trans-lactone 10 resonated at δ3.60 (dd, $J_{2,3}$=10.8 Hz, $J_{3,4}$=3.9 Hz), while the C_5-proton absorbed a δ3.18 (dd, $J_{4,5}$=6.6 Hz, $J_{5,6}$=3.8 Hz).

Equilibration (t-BuOK, t-BuOH, Et_2O, 25°C) of lactones 9 and 10 gave a readily separable (flash chromatography) 1:1 mixture. However, deprotonation (LDA, THF, –78°C) of either lactone followed by kinetic protonation (HOAc) gave a 19:1 ratio of 9/10. Protonation occurs preferentially on the sterically less demanding face of the lactone enolate. Ozonolysis of olefinic acetonide 11 (O_3, $MeOH/CH_2Cl_2$, $NaHCO_3$, –78°C) followed by reduction ($LiAlH_4$, Et_2O) afforded alcohol 13 in 83% yield.

Alcohol 13 is a chiral, non-racemic synthon (%ee>99.9)[2] for the erythronolides having the absolute stereochemistry of carbons 2-6 correlating with their counterparts in 6-deoxyerythronolide B (5b).

ACKNOWLEDGMENTS

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REFERENCES AND NOTES

1. This communication is dedicated to Professor Gilbert Stork on the occasion of his sixty-fifth birthday.

2. a) F. E. Ziegler, A. Kneisley, and R. T. Wester, Tetrahedron Lett., 1986, 27, 1221; b) F. E. Ziegler and R. T. Wester, ibid., 1986, 27, 1225; c) F. E. Ziegler, E. P. Stirchak, and R. T. Wester, ibid., 1986, 27, 1229; d) F. E. Ziegler and A. Kneisley, ibid., 1985, 26, 263 and earlier references cited therein.

3. For a recent synthesis of an erythronolide fragment, see S. D. Burke, F. J. Schoenen, and C. W. Murtiashaw, Tetrahedron Lett., 1986, 27, 449; M. Kinoshita, M. Arai, K. Tomooka, and M. Nakata, ibid., 1986, 27, 1811. For previous syntheses of erythromycin, erythronolides, and fragments thereof, see references 2 and 4, respectively, in these papers.

4. Diisobutylaluminum hydride (DIBAL) was used instead of $LiAlH_4$ to cleave the acetates.

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