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STEREOSELECTIVE METHYLATION OF β-HYDROXYLACTONE DIANIONS

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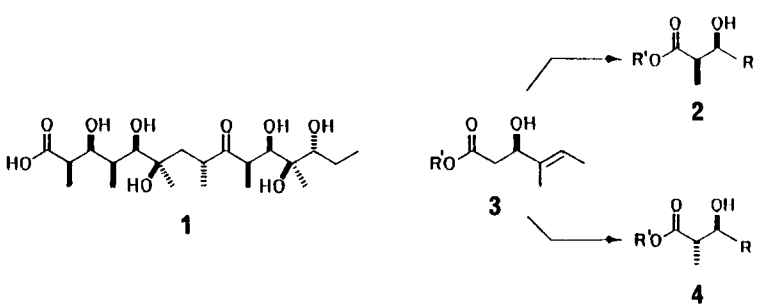
Summary: 3-Alkoxy enolates of γ-butyrolactones are stereoselectively methylated at C-2 to give the corresponding trans-3-hydroxy-2-methyl-γ-butyrolactones.

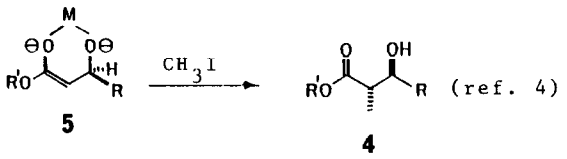
As part of a projected synthesis of poly-hydroxy antibiotic precursors such as Erythronolide A seco acid, 1, we are investigating ways of producing optically active erythro-3-hydroxy-2-methylalkenoates (2) which do not involve the stereoselective aldol methods reported recently by number of groups.[1] Instead, we have chosen to study a route by which the chiral alcohol center in esters such as 3 is used as a control element to induce stereoselective methylation at C-2. The rationale of this approach is that the optically active precursor 3



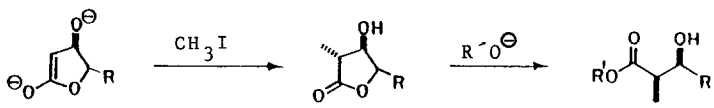
should be readily available from the racemate by use of the newly-developed Sharpless kinetic resolution process.[2] Since racemic 3 is obtained by simple condensation of ester enolates with α,β-unsaturated aldehydes (many of which are commercially available and inexpensive), this strategy would have considerable merit if an erythro-selective methylation procedure were available. In this communication we report some preliminary results on the alkylation of lactone enolates derived from 3 as a means of achieving this goal.

The formation of 3-alkoxy ester enolates has been known for a number of years.[3] Methylation of such dianions gives mainly (~98%) the threo-ester (4) containing only minor amounts (~2%) of the erythro-isomer, 2.[4] The observed stereoselectivity is attributed to a chelation effect which results in the

shielding of one face of the enolate by the R group, as in 5. We reasoned that the other face of the enolate (relative, of course, to the 3-hydroxy group) would be shielded in the corresponding lactone dianion 6. Methylation from the side opposite the alkoxide group to give 7 followed by alcoholysis of the lactone ring would produce the erythro-isomer corresponding to 2. During our testing of this hypothesis, a study of the alkylation of 3-hydroxy-γ-butyrolac-

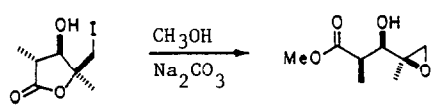


5 4



6 7 8

tone dianion (6, R=H) was published[5] which confirms this stereochemical prediction. However, that report states that the simple lactone dianion cannot be methylated on carbon without concurrent methylation of the 3-alkoxy group, a problem which obviously limits the usefulness of the reaction. In direct contrast to that result, we have succeeded in monomethylating several relatively complex β-hydroxy lactones, examples of which are shown in the Table. Additives such as HMPT are not required,[6] and the reaction can be run on a fairly small scale, using excess base (LDA) and methyl iodide, without concurrent methylation of the 3-hydroxy group.[7] The yields are good (except in the case where iodide elimination is a serious competing process during dianion formation), and HPLC analysis of the crude reaction mixtures[8] indicates that the ratio of 2,3-trans to 2,3-cis products is consistently ca. 10:1. Finally, we have verified in one case that lactone alcoholysis can be accomplished without epimerization of the newly introduced 2-methyl group.



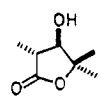
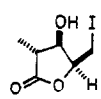
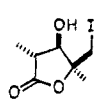
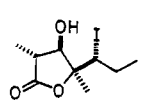
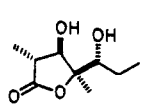
2α/2β = 9/1 (2,3)Erythro/(2,3)Threo = 9/1

Three lines of evidence were used in determining the lactone stereochemistries. The methylated iodolactones were compared spectrally and chromatographically with authentic products prepared by iodolactonization[9] of the appropriate erythro- or threo-3-hydroxy-2-methyl-4-alkenoic acids.[10] The other products were identified using a combination of ^{13}CMR and ^{1}HMR. In particular, the ^{13}CMR chemical shift of the C-2 methyl group of each major isomer is found in the

10.5-13.5 ppm range reported for similar lactones, whereas in the minor isomer it is shifted upfield by 4-5 ppm due to shielding by the cis-hydroxyl group.[11] The major isomer in each case also exhibits a larger 2H,3H ^{1}HMR coupling constant than the minor isomer (see Table), in accord with data on structurally related lactones published by Heathcock.[11]

The reactions reported in this Communication illustrate that a 3-hydroxy group in γ-butyrolactones does exert a synthetically useful level of stereochemical control during methylation at the 2-position, and that competitive O-methylation is not a serious side-reaction. Applications of this strategy to the synthesis of optically active natural products will be reported later.

TABLE. Methylation of Lactone 3-Alkoxyenolates.

Major Product (2α)	Product Ratio 2α/2β	H-2,3 Coupling (Hz) 2α/2β	Isolated Yield
	93/7	9.8/5.4	79%
	93/7	5.2/4.8	67%
	91/9	8.8/5.3	70%
	-	-	25%
	88/12	7.4/ -	84%

Acknowledgements:

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References

1. We utilize Heathcock's convention for designating threo- and erythro-isomers.[1c] Recent examples of stereo- and/or enantioselective aldol reactions include: a) Evans, D.A.; Bartroli, J.; Shih, T.L. J. Am. Chem. Soc.

1981, 103, 2127 and references cited, b) Masamune, S.; Choy, W.; Kerdesky, F.A.J.; Imperiali, B. J. Am. Chem. Soc. 1981, 103, 1566 and references cited, c) Pirrung, M.C.; Heathcock, C.H. J. Org. Chem. 1980, 45, 1727 and references cited, d) Bartlett, P.A. Tetrahedron 1980, 36, 2.

2. Martin, V.S.; Woodard, S.S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K.B. J. Am. Chem. Soc. 1981, 103, 6237.

3. Herrmann, J.L.; Schlessinger, R.H. Tetrahedron Lett. 1973, 2429.

4. a) Seebach, D.; Wasmuth, D. Helv. Chim. Acta 1980, 63, 197, b) Frater, G. Helv. Chim. Acta 1979, 62, 2825.

5. Shieh, H.-M.; Prestwich, G.D. J. Org. Chem. 1981, 46, 4319.

6. Hexamethylphosphoric triamide (HMPT) was used in the alkylations described in reference 4 (but not reference 3), and was reported to be necessary for the lactone C-alkylations described in reference 5.

7. A representative procedure, for entry 1 in the Table, is as follows: To a dry flask containing 3.85 mmol of lithium diisopropylamide (prepared from 3.85 ml, .55 mmol, diisopropylamine and 2.43 ml, 3.85 mmol, of 1.59 M n-butyllithium) in 4 mL THF at -78°C was added a solution of 5,5-dimethyl-4-hydroxytetrahydro-2-furanone, (121 mg, .93 mmol) in 3 mL THF. After 1h at -78°C the resulting solution was transferred by cannula to a stirred, -78°C solution of 1.6 mL (3.6 g, 25 mmol) of methyl iodide in 20 mL THF. After 2 h the reaction was quenched with .21 mL (.22 g, 3.68 mmol) glacial acetic acid in 5 mL THF. The reaction mixture was allowed to warm to room temperature and then diluted with saturated aqueous sodium bicarbonate, extracted with ether (3 x 20 mL), and dried over anhydrous sodium sulfate. Removal of solvents in vacuo yielded 196 mg (147%) of crude product. Flash chromatography (5 g SiO_2, 7:1 ether:petroleum ether gave 97.6 mg (73%) of a less polar (Rf = .61, Et_2O) major isomer and 7.8 mg (6%) of a more polar (Rf = .50, Et_2O) minor isomer. Major isomer: mp 55-56°C; HPLC retention time 6.5 min; ^1H NMR (250 MHz, $CDCl_3$) δ 1.26 (d, J = 7.1, 3H), 1.32 (s, 3H), 1.42 (s, 3H), 2.64 (dq, J = 7.1, 9.8, 1H), 3.65 (br.s, 1H), 3.79 (d, J = 9.8, 1H); IR ($CDCl_3$) 3430 (OH), 29787, 2930, 2870, 1755 (C=O)), 1460, 1375, 1305, 1260, 1240, 1120, 1090, 1070, 1050 cm^{-1}; ^{13}C NMR (250 MHz, $CDCl_3$) δ 12.8, 20.89, 26.71, 42.04, 81.14, 85.09, 177.04. Minor isomer: HPLC retention time 7.6 min; ^1H NMR (250 MHz, $CDCl_3$) δ 1.27 (d, J = 7.2, 3H), 1.38 (s, 3H), 1.47 (s, 3H), 2.96 (dq, J = 7.2, 5.4, 1H), 4.06 (d, J = 5.4, 1H); IR ($CDCl_3$) 3420 (OH), 2980, 2970, 2930, 2870, 1755 (C=O), 1460, 1450, 1370, 1380, 1260, 1090; ^{13}C NMR (250 MHz, $CDCl_3$) δ 8.4, 21.9, 25.7, 40.4, 76.0, 85.7, 177.8.

8. HPLC ratios were obtained using a Waters μ-Porasil column with hexane-ether mixtures as eluent. Iodine-containing lactones were detected at 254 nm and the others at 214 nm. The HPLC ratios were corroborated by 250 MHz NMR spectra, which showed small amounts (~ 10%) of the minor, isomeric products.

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10. The threo-isomers were prepared according to reference 4 using as starting material the appropriate ethyl-3-hydroxy-4-alkenoates. The erythro-isomers were isolated from diasteriomer mixtures obtained by condensing ethyl lithiopropionate with the appropriate commerically available α,β-unsaturated aldehyde.

11. Heathcock, C.H.; Young, S.D.; Hagen, J.P.; Pirrung, M.C.; White, C.T.; VanDerveer, D. J. Org. Chem. 1980, 45, 3846.

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