Tetrahedron Letters,Vol.25,No.30,pp 3171-3174,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

DIRECT SYNTHESIS OF PYRAN-LACTONES RELATED TO NAPHTHOQUINONE ANTIBIOTICS

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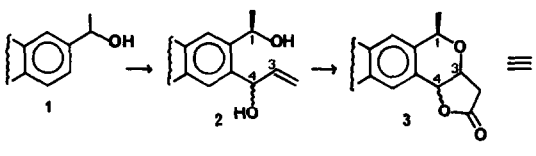
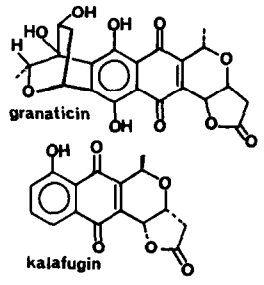
Abstract. Simple benzopyrans with a fused γ-lactone unit are prepared from an o-disubstituted arene by direct intramolecular alkoxycarbonylation/lactonization promoted by palladium diacetate; the process gives high yields and moderate stereoselectivity, favoring the cis lactone over trans by a factor of 5:1.

The fused pyran-γ-lactone structural feature appears in a number of interesting natural structures such as kalafugin[2] and granaticin.[3] Utilizing the efficient pyran and furan ring-forming process termed alkoxy-carbonylation,[4,5] and based on the direct metalation techniques of Seebach,[6] a simple strategy presents itself for a two-step generation of the

SCHEME 1. Strategy

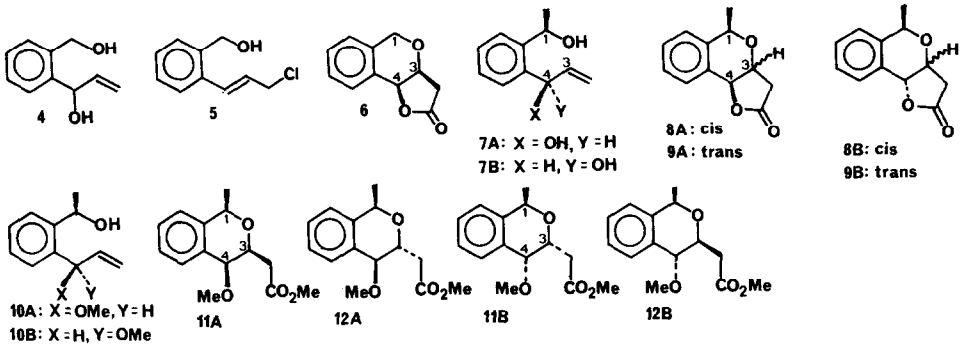




typical pyran-lactones (Scheme 1). Important technical questions need to be resolved concerning efficient trapping of the aryllithium from 1 with acrolein, diastereoselectivity in formation of 2 and possible sensitivity of the allylic hydroxyl toward cleavage. A central question is the influence of the allylic hydroxyl and the methyl at C-1 on the configuration of the new chiral center (C-3) in 3.[7] In simple pyran ring formation, a preference toward a cis arrangement of the 2,6-substituents has been noted.[4,5]

The first model (4) was obtained in one step from o-bromobenzyl alcohol by lithiation and quenching with acrolein (77% yield). Under the standard conditions for catalytic alkoxycarbonylation (0.1 mol-eq. of $PdCl_2$, 3.0 mol-eq. of $CuCl_2$, CO at 1.1 atm) but in THF instead of methyl alcohol, the only product isolated (74% yield) was the rearranged chloride, 5. The

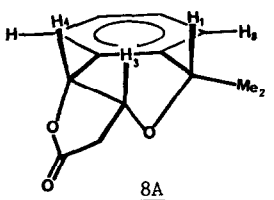
desired cyclization was successful using 1.0 mol-eq. of palladium diacetate in THF with 1.1 atm of CO. A single isomer (6) was obtained in 68% yield after chromatography.[8,9] The skeleton and configuration (cis ring fusion) were verified by ^1H NMR double resonance experiments in comparison with natural product structures.[10]



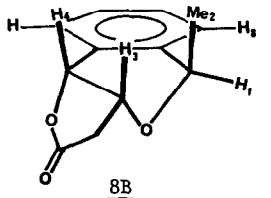
In order to test for the influence of remote substituents on the stereoselectivity, the diastereomeric diols 7A and 7B were prepared. Lithiation[6] of α-phenethyl alcohol with n-butyllithium followed by addition to acrolein produced a mixture of 7A/7B (50:50) which was easily separated by column chromatography. The isomers were obtained in greater than 98% diastereomeric purity.[8] Cyclization of 7A (configuration assigned in retrospect, from the structure of the product) with 1.0 mol-eq. of palladium diacetate, as before, gave two products, in isolated yields of 64% and 13%. The major product was identified as the cyclization product with a cis-fused γ-lactone (8A)[8,11] while the minor product showed general similarity but key differences in the spectral data, and is assigned as the trans-lactone (9A).[8,11] The primary structure elucidation technique is proton NOE measurement. For example, the configuration and conformation for 8A follows directly from the NOE results shown in figure 1. The cyclization of diastereomer 7B also led to two products, with isolated yields of 70% and 14%. The major isomer again bears the cis-fused γ-lactone (8B)[8,12] now with a trans-methyl group at C-1, while the minor isomer shows spectral data consistent with the trans-lactone, 9B.[8,12] For the NOE evidence concerning 8B, see fig. 1.

Positive NOE:
Me_2-H_8; Me_2-H_1

No NOE:
Me_2-H_3; Me_2-H_4



8A



8B

Positive NOE:
Me_2-H_1; Me_2-H_3;
Me_2-H_4.

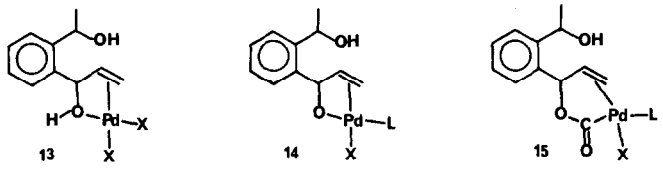
No NOE:
Me_2-H_8

FIGURE 1. Nuclear Overhauser Enhancements

To assay the possibility that the stereoselectivity in cyclizations of 8A and 8B is the result of coordination of the allylic hydroxyl group, the diastereomeric monomethylethers (10A/10B) of diols 8A/8B were prepared and separated. Cyclization of 10A (stoichiometric palladium diacetate, but methyl alcohol solvent) produced a 100:94 mixture of pyrano-esters (11A, 12A; 94% yield) which could be separated by careful chromatography. The isomers showed

nearly identical spectral data, but relative configurations could be assigned from NOE studies.[8,13] Cyclization of diastereomer 10B gave a mixture of pyran-esters (11B, 12B) in the ratio 6:5 (91% yield together). After tedious chromatographic separation, samples of each isomer in high purity were obtained. Parallel with the analysis for 11A and 12A, the structures were assigned as shown above.[8,14]

The results with the free allylic hydroxy compound compared to the corresponding methyl ethers suggests a strong directing effect of the allylic hydroxyl, favoring formation of a cis-lactone irrespective of the configuration of the methyl group at C-1. The directing effect observed here could arise through coordination of the hydroxyl with Pd(II) as in 13, of alkoxide (as in 14), or of alkoxyacyl (as in 15). Intermediate 15 requires a reductive-elimination of an acyl-alkyl palladium intermediate in the final step rather than the proposed hydroxy-acyl coupling.[15]



L = neutral donor ligand

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7. For examples of allylic amino, phosphino, and thioether directing groups in intermolecular nucleophilic addition promoted by Pd(II), see: (a) Hegedus, L.S.; Siirala-Hansen, K. J. Am. Chem. Soc. 1975, 97, 1184; (b) Holton, R.; Kjonaas, R. J. Organomet. Chem. 1977, 133, C5; (c) Haszeldine, R.N.; Lunt, R.J.; Parrish, R.V. J. Chem. Soc. A, 1971, 3705. (d) Medema, D.; VanHelden, R.; Kohll, C.F. Inorg. Chim. Acta, 1969, 3, 255. We are aware of no examples with an allylic hydroxyl group.

8. Consistent IR, ^{13}C NMR, MS, and analytical data have been obtained.

9. For compound 6. ^{1}H NMR($CDCl_3$): δ 2.80(m, 2H, AB of an ABX system, 2H at C-3), 4.42-4.53(m, 1H, H-3), 4.74(d, 2H, J=2.0 Hz, 2H at C-1), 5.19(d, 1H, J=3.3 Hz, H-4), 7.05-7.60(m, 4H, Ar-H). Irradiation at δ 2.95 gave the following partial spectrum: δ 4.56(d, 1H, J=3.3 Hz), 4.82(d, 2H, J=1.9 Hz), 5.26(d, 1H, J=3.3 Hz). Mp 116-117°C.

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11. For 8A: ^{1}H NMR($CDCl_3$): δ 1.58 (d, 3H, J=6.5 Hz, CH_3), 2.86 (2H, AB part of an ABX system with δ_A=2.76, δ_B=2.96, J_{AB}=17.5 Hz, J_{AX}=0.0 Hz, J_{BX}=5.0 Hz, 2H at C-3), 4.50-4.58 (m, 1H, H-3), 4.71 (q, 1H, J=6.3 Hz, H-1), 5.18 (d, 1H, J=3.1 Hz, H-4), 7.2-7.5 (m, 4H, Ar-H). The signal at δ 1.58 was irradiated and the following signal enhancements observed (multiplicity and relative intensity in parentheses): 4.71 (m, 0.8), 7.22 (m, 1.0). Mp 109-110°C.

For 9A: ^{1}H NMR($CDCl_3$): δ 1.56 (d, 3H, J=6.8 Hz, CH_3), 2.61-2.86 (2H, AB part of an ABX system, 2H at C-3), 3.91-4.02 (m, 1H, H-3), 4.88 (d, 1H, J=9.1 Hz, H-4), 5.14 (q, 1H, J=6.8 Hz, H-1), 7.04-7.08 (m, 1H, H-8), 7.18-7.46 (m, 3H, H-5,6,7). Irradiation of the signal at δ 1.56 resulted in peak enhancements at 4.00, 5.14, and 7.06. Irradiation of the signal at 4.00 resulted in peak enhancement at 2.7. Irradiation of the signal at 4.88 resulted in peak enhancement at 2.7. Irradiation at δ 5.14 resulted in peak enhancement at 1.56 and 7.06.

12. For 8B: ^{1}H NMR($CDCl_3$): δ 1.51 (d, 3H, J=7.0 Hz, CH_3), 2.75(2H, AB part of an ABX system with δ_A=2.64, δ_B=2.97, J_{AB}=17.8 Hz, J_{AX}=0.9 Hz, J_{BX}=5.1 Hz, 2H at C-3), 5.02 (q, 1H, J=7.0 Hz, H-1), 5.17 (d, 1H, J=3.3 Hz, H-4), 7.0-7.5 (m, 4H, Ar-H). Irradiation at 1.51 gave selective signal enhancement (multiplicity and relative intensity in parentheses): 4.77 (m, 0.70), 5.02 (m, 1.0), 5.17 (d, 0.3). Mp 109-110°C.

For 9B: ^{1}H NMR($CDCl_3$): δ 1.49 (d, 3H, J=6.6 Hz, CH_3), 2.68-2.86 (2H, AB part of an ABX system, 2H at C-3), 3.88-3.99 (m, 1H, H-3), 4.92(d, 1H, J=9.1 Hz, H-4), 5.13 (q, 1H, J=7.0 Hz, H-1), 7.02-7.06 (m, 1H, H-8), 7.18-7.33 (m, 3H, H-5,6,7). Irradiation at δ 1.49 resulted in enhancement of the signals at 5.13 and 7.04. Irradiation at δ 3.9 resulted in enhancement at 2.75 and 5.13. Irradiation at δ 4.92 resulted in enhancement of the signal at 2.75. Irradiation at δ 5.13 resulted in enhancement of the signals at 1.49, 3.9 and 7.04.

13. For 11A: ^{1}H NMR($CDCl_3$): δ 1.56 (d, 3H, J=6.5 Hz, CH_3), 2.87 (d, 2H, J=6.7 Hz, 2H at C-3), 3.34 (s, 3H, OCH_3), 3.73 (s, 3H, $COOCH_3$), 4.13-4.19 (m, 2H, H-3, H-4), 4.84 (q, 1H, J=6.5 Hz, H-1), 7.17 (d, 1H, J=7.5 Hz, H-8), 7.17-7.35 (m, 2H, H-6, H-7), 7.35-7.40 (m 1H, H-5). Irradiation at δ 3.34 resulted in enhancement of peaks at 4.18, 7.35. Irradiation at δ 4.84 resulted in signal enhancement at 4.18, 7.17 and 1.56. Irradiation at δ 2.87 resulted in signal enhancement at 4.18. Irradiation at δ 1.56 resulted in signal enhancement at 7.17 and 4.84.

For 12A: ^{1}H NMR($CDCl_3$): δ 1.54 (d, 3H, J=6.6 Hz, CH_3), 2.65 (2H, AB of an ABX system with δ_A=2.59, δ_B=2.71. J_{AB}=15.0 Hz, J_{AX}=10.0 Hz, J_{BX}=5.0 Hz, 2H at C-3), 3.48 (s, 3H, OCH_3), 3.73 (s, 3H, $COOCH_3$), 4.17 (d, 1H, J=6.1 Hz, H-4), 4.44-4.52 (m, 1H, H-3), 4.94 (q, 1H, J=6.6 Hz, H-1), 7.03-7.06 (m, 1H, H-8), 7.24-7.28 (m, 2H, H-6, H-7), 7.37-7.40 (m, 1H, H-5). Irradiation at δ 3.48 resulted in the enhancement of signals at 7.38, 4.48 and 4.17. Irradiation at δ 1.54 resulted in the enhancement of signals at 7.05, 4.94, 4.48. Irradiation at δ 4.17 resulted in the enhancement of the signal at 7.38 and 2.65.

14. For 11B: ^{1}H NMR($CDCl_3$): δ 1.48 (d, 3H, J=6.8 Hz, CH_3), 2.76 (m, 2H, C-3), 3.38 (s, 3H, OCH_3), 3.73 (s, 3H, $COOCH_3$), 4.19 (d, 1H, J=2.6 Hz, H-4), 4.49 (dt, 1H, J=6.7 Hz, 2.5 Hz, H-3), 5.08 (q, 1H, J=6.7 Hz, H-1), 7.08 (d, 1H, J=7.8 Hz, H-8), 7.20-7.30 (m, 2H, H-6, H-7), 7.30-7.35 (m, 1H, H-5). Irradiation at δ 4.19 resulted in peak enhancements at 7.31, 3.38, and 2.76. Irradiation at δ 3.38 resulted in enhancements of the signals at 7.31, 4.19. Irradiation at δ 1.48 gave peak enhancements at 7.08, 5.08, and 4.49.

For 12B: ^{1}H NMR($CDCl_3$): δ 1.48 (d, 3H, J=6.5 Hz, CH_3), 2.75 (2H, AB of an ABX system with δ_A=2.62, δ_B=2.89, J_{AB}=17.5 Hz, J_{AX}=10.0 Hz, J_{BX}=2.5 Hz, 2H at C-3), 3.44 (s, 3H, OCH_3), 3.74 (s, 3H, $COOCH_3$), 4.13 (dt, 1H, J=9.0 Hz, 3.7 Hz, H-3), 4.37 (d, 1H, J=9.2 Hz, H-4), 4.88 (q, 1H, J=6.7 Hz, H-1), 7.05-7.09 (m, 1H, H-8), 7.22-7.30 (m, 2H, H-6, H-7), 7.43 (m, 1H, H-5). Irradiation at δ 4.37 resulted in an enhancement of the signals at 7.37, 3.44 and 2.75. Irradiation at δ 3.44 resulted in an enhancement of the signals at 7.34, 4.37, 4.13. Irradiation at δ 1.48 resulted in enhancement of the signals at 4.88 and 7.07.

15. We are pleased to acknowledge support of this work by the National Institutes of Health (GM 31352), and the National Science Foundation (for a Departmental grant for the purchase of the NMR equipment), and the Johnson-Matthey Corporation for gifts of palladium salts.

(Received in USA 30 April 1984)