Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 23 Sep 2006.

To cite this article: Tomas Hudlicky, Michael G. Natchus & Thomas C. Nugent (1992) Improved Practical Synthesis of a Prostaglandin and Carbocyclic Nucleoside Synthon, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 22:1, 151-157, DOI: 10.1080/00397919208021086

To link to this article: http://dx.doi.org/10.1080/00397919208021086

SYNTHETIC COMMUNICATIONS, 22(1), 151-157 (1992)

Improved Practical Synthesis of a Prostaglandin and Carbocyclic Nucleoside Synthon

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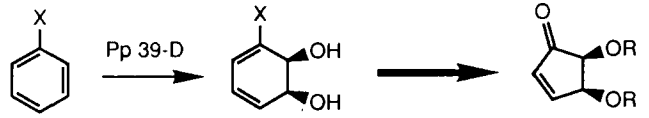
Abstract: An efficient, four step synthesis of chiral enone **2a** [(+)-2,3-(isopropylidenedioxy)-4-cyclopentenone] from diol **1a** (X = Cl), available from microbial oxidation of chlorobenzene, is described. This synthesis is a vast improvement over that previously reported and compares very favorably with others in the literature.

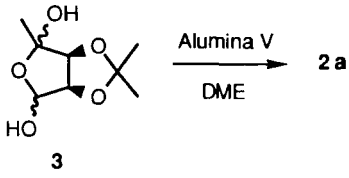
Biocatalysis is rapidly gaining acceptance in the chemical community as a source of chiral pool synthons for organic synthesis. Our recent work has focussed on microbial oxidation of substituted arenes, originally discovered by Gibson,[2] as a route to enantiomericly pure cis arene diols of type **1**.[3] Such work has led to preparation from toluene of (+) enone **2a**[3] which served as starting material for the total synthesis of prostaglandin $PGE_{2\alpha}$.[4] Previous syntheses of **2a,b** have relied upon resolution of racemic materials,[4] enzymatic processes,[5] or use of sugars[6-11] as sources of chirality. These compounds have enjoyed widespread popularity as precursors to prostaglandins[4] and carbocyclic nucleosides of the Neplanocin A type.[5,6,8] Herein we describe an alternate and improved approach to **2a** from chlorobenzene diol **1a**.



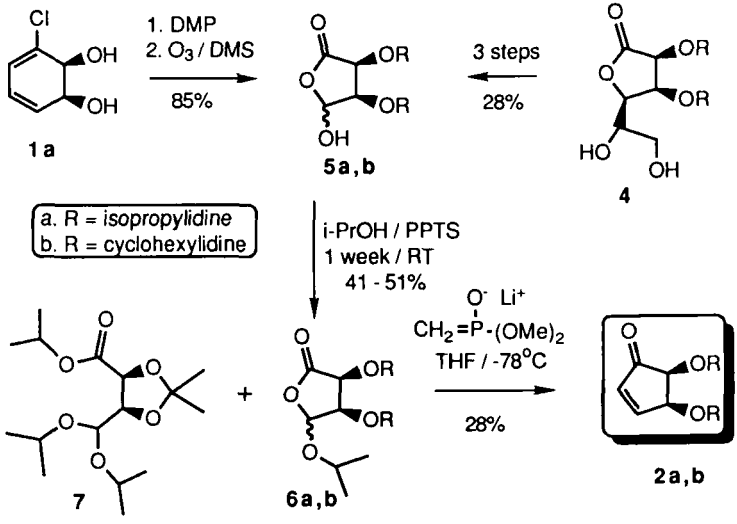
1a X = Cl
1b X = Br
1c X = CH_3

2a R = $C(CH_3)_2$
2b R = $C(CH_2)_5$

In the previous preparation of **2a**[3] a mixture of hemiacetals **3** generated from toluene diol was dehydrated to **2a**. Such dehydrations of carbonyl compounds have been reported using alumina;[12-14] however, we have experienced difficulty in preparing the catalyst with reproducible activity. This resulted in inconsistent yields for the transformation of **3** to **2a** (5 - 65%). Development of an alternative and reproducible route to **2a** from an alternate arene diol source became nessecary .



Borchardt reported a synthesis of (-) **2b** from D-gulanolactone **4** which proceeded through hydroxylactone **5b**.[6,7] The recently reported analog **5a** was prepared from chlorobenzene diol **1a** and used in enantiodivergent syntheses of (+) and (-) trihydroxyheliotridane,[15] (+) and (-) erythrose,[16] and ribonolactone.[17] As the



preparation of **5a** from **1a** was more efficient than the sugar route originating in **4**, it seemed ideal to intercept the Borchardt synthesis.

Table 1 Formation of Hemiacetal **7a**

CONDITIONS	% YIELD **6a**	% YIELD **7**
CH_3CO_2H / i-PrOH / reflux / 1.5hr	17	8
p-TsOH / i-PrOH / reflux / 1.5hr	23	15
PPTS / i-PrOH / reflux / 1.5hr	21	12
PhH / p-TsOH / i-PrOH / reflux /1.5hr / mol.sieves	19	11
PPTS / i-PrOH / RT / 1 week	41 - 51	9
PPTS / iPrOH / 0°C / 1 month	0	0
$HClO_4$ / iPrOH:acetone (1:3) / 4°C / 24 hr	36	>5

A number of reaction conditions were investigated for the acid catalyzed conversion of **5a** to **6a** and these are summarized in Table 1. Acetal **7** was usually present as a minor byproduct, and could be easily separated from desired **6a** via flash chromatography. The yield of **7a** obtained from chlorobenzene compares favorably with that obtained by the sugar route. The major operational difference is the presence of acid labile isopropylidine group, which however offers advantage of easy removal over the cyclohexylidine.[18] Optimum conditions were realized by letting **5a** stand in isopropanol with pyridinium p-toluenesulfonate at room temperature for 1 week to give consistent yields of 41 - 51% of **6a**. The Wittig transformation of **6a** to **2a** was carried out as described by Borchardt[7] and proceeded in 28% rather than the reported 80% yield. We were not able to improve the yield of this reaction.

In summary, a short, reproducible synthesis of enone **2a** from chlorobenzene diol **1a**[19] has been accomplished in 5 steps (4 operations) in 12% overall yield. In view of our experience with the repetition of some of the published procedures, this is a yield superior to our own preparation from toluene[3] as well as to those procedures we have had the occasion to repeat.[20] Enone **2a** is an intermediate in the total synthesis of (-)-Specionin which will be reported in due course elsewhere.

Experimental Section

Analytical TLC was performed on silica gel 60F-254 plates (EM Science). Flash chromatography was performed on Kieselgelm 60 (EM Science, 230-400 mesh).

Infrared spectra were recorded on a perkin Elmer 283B, 710B, or a 1600 series FT-IR instrument. ^{1}H-NMR spectra were obtained from a Bruker WP-200 or WP-270 instrument. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane as an internal standard (0.00ppm).

2,3-(Isopropylidenedioxy)-4,4-dihydroxybutanic Acid Lactone (5a). Chlorobenzene diol **1a** (1.00 g, 6.83 mmol) was dissolved in 10 ml of acetone and 3 ml. of 2,2-dimethoxypropane and stirred with 50 mg of para-toluenesulfonic acid at room temperature for 1 h whereupon it was neutralized with 1 mL of $NaHCO_3$ (sat) and evaparated to dryness. The crude oil was taken in 100 mL of ether and washed with water and then brine, dried over $MgSO_4$, filtered and evaparated to give 1.22 (6.58 mmol, 96 %) of clear oil. The crude mixture was taken in 100 mL of ethyl acetate.and cooled to -78 °C. Oxygen was bubbled through the mixture for 5 min. followed by ozone enriched oxygen for about 20 min. until the solution turned deep blue, and then oxygen again for 5 min. until the mixture was again clear. Dimethyl sulfide (15 mL) was added to the solution and the entire reaction vessel was stored overnight at -20 °C. The mixture was then evaparated to dryness, taken in ether (100 mL) and washed with water and brine. The organic layers were dried over $MgSO_4$, filtered, and evaparated to give 1.02 g of crude hydroxylactone **5a** which is sufficiently clean for the next step. Purification over 10 % deactivated silica gel with hexane:ethyl acetate (2:1) delivered a white solid, mp = 102 - 104 °C (lit. = 103 - 104 °C)[21] which matched those previously reported in the literature

2,3-(Isopropylidinedioxy)-4-hydroxy-4-(2-propyloxy)-butanoic acid (5a) Method 1. Hydroxylactone **5a** (1.01 mg, 5.80 mmol) was dissolved in 2-propanol (100 mL) and stirred at room temprature with 100 mg of pyridinium p-toluenesulfonate for 1 week whereupon the mixture was neutralized with 1 mL of $NaHCO_3$ sat and solvent removed under vacuum. The residue was taken in ether (100 mL) and washed with water and then brine. The organic layers were dried over $MgSO_4$, filtred and evaparated to give xx mg of crude oil which was purified over 10 % deactivated silica gel to give 0.514 g (2.38 mmol, 41%) of pure **6a** whose spectral properties matched those previously published. (IR, NMR).[7] $[\alpha]_D$ = -34.6°. mp = 36 °C. **Method 2.** Hydroxylactone **5a** (1.03 mg, 5.92 mmol) was dissolved in 75 mL of acetone and 25 mL of 2-propanol and chilled in the

refrigerator to 4 °C whereupon $HClO_4$ (70 %, 100 µl) was added and the mixture placed back in the refrigerator for 24 hours. The solution was then neutralized with 1 ml of $NaHCO_3$ sat. and worked up as in method 1 to deliver 0.460 g (2.13 mmol, 36%) of pure **6a.**

2,3-(isopropylidinedioxy)-4-cyclopentenone 2a. Dimethyl methyl phosphonate (672 µL, 6.20 mmol) was added via syringe to 10 mL of dry THF under argon and cooled to -78 °C followed by slow addition of n-butyl lithium (2.58 mL, 2.4 M in hexanes, 6.20 mmol) via syringe. The solution became noticeably cloudy. This mixture was stirred at -78 °C for 15 min.whereupon isopropoxy lactone **6a** (1.03 g, 4.77 mmol) was added via cannula in 4 mL of dry THF. The resulting mixture was stirred for 20 min. at -78 °C and then allowed to warm to room temperature over 1 h at which time the reaction was quenched with NH_4Cl (sat.) and partitioned between water (10 mL) and ether (100 mL). The layers were separated and the organic layer extracted 1x with water and brine. The organic layer was then dried over $MgSO_4$, filtered and evaparated to give 640 mg of crude oil. The residue was chromatographed over 10% deactivated silica gel with hexane : ethyl acetate (3 : 1, 2 : 1) as eluant to give 205 mg (1.34 mmol, 28%) of pure enone **2a** as white crystals; **mp** 41 - 42 °C (lit.[3] mp 42 °C); $[\alpha]^{25}_D$ +63.4° (*c* 1.12, $CDCl_3$) (lit.[3] $[\alpha]^{25}_D$ +62.8° (c 0.7, $CDCl_3$)), **IR** (KBr pellet) 3000, 2940, 1730, 1380 cm^{-1}; **^{1}H NMR** ($CDCl_3$) d 7.65 (dd, J_1 = 5.9, J_2 = 2.2 Hz, 1H), 6.22 (d, J = 5.9 Hz, 1H), 5.27 (dd, J_1 = 5.5, J_2 = 2.2 Hz, 1H), 4.46 (d, J = 5.5 Hz, 1H), 1.42 (s, 6H).

Acknowledgements. The authors express their gratitude to Professor Borchardt and members of his group for helpful discussions and to the following agencies for their generous support: American Chemical Society, PRF (AC-16617, AC-20748), National Institutes of Health (AI-00564, AI-19749), and the Jeffress Trust Fund.

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(18) We have experienced difficulty in deprotecting the cyclohexylidine group in **2b** (prepared by Borchardt's route) and compounds derived from it using various reported procedures.

(19) Chlorodiol **1a** as well as the bromo-derivative are commercially available from Genencor, Int., Rochester, NY and ICI Fine Chemicals, Manchester, UK. It can also be easily prepared according to the procedure found in reference 3 using Gibson's Pp 39D. (For sources of this bacterium, contact Professor David Gibson, Dept. of Microbiology, University of Iowa).

(20) We have repeated three of the syntheses published. Below is the tabulation of overall yields that were reported versus the yields that we were able to obtain by repetition in the number of repetitions listed.

Reference #	Reported Yield(%)	Repeated Yield(%)	# of Trials
3	45	~4	10
6	18.5	~5	5
7	44.5	~6	2
this work	12	12	10

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(Received in US 11 July, 1991)