Tetrahedron Letters No. 10, pp 765 - 768, 1975. Pergamon Press. Printed in Great Britain.

PROSTAGLANDINS AND CONGENERS VIII[1]. AN IMPROVED PROCEDURE FOR THE CONJUGATE ADDITION OF 3-OXY-E-1-ALKENYL LIGANDS VIA LITHIUM ALANATE REAGENTS. 11-DEOXYPROSTAGLANDIN E_1 ANALOGUES

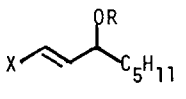
Karel F. Bernady, John F. Poletto, and Martin J. Weiss

Lederle Laboratories, Pearl River, New York 10965

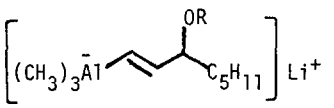
(Received in USA 8 January 1975; received in UK for publication 27 January 1975)

Recent communications from these laboratories have described a new and useful procedure for the synthesis of prostaglandins based upon the conjugate addition to cyclopentenones of E-1-alkenyl ligands from lithium E-1-alkenyltrialkylalanate reagents.[2] The preparation of these alanate reagents requires diisobutylaluminum hydride reduction of terminal acetylenes. This reaction is disadvantageous with propargylic ethers, for these may not necessarily undergo the expected cis-wise hydroalumination[2b] and furthermore may suffer reductive cleavage of the carbon-oxygen bonds. We now wish to report an improved alanate procedure for the 1,4-transfer of 3-oxy-E-1-alkenyl ligands, which eliminates the preparation of the alanate reagents via hydroalumination of propargylic ethers.

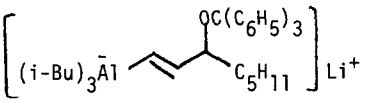
3-Oxy-E-1-alkenyllithium reagents may be obtained almost quantitatively by alkyllithium-alkenyl iodide exchange reactions.[3] We have found that the ate complexes formed by treatment of these alkenyllithiums with trialkylaluminums also conjugatively transfer the alkenyl ligands to cyclopentenones in good yield. Accordingly, 1-iodo-E-1-octen-3-ol (1),[3] protected as the p-anisyldiphenylmethyl ether 2, was metalated (toluene, 1 g/ml) with 1 equivalent of n-butyllithium in hexane (-40^0, 2 hr) to yield octenyllithium 3. Addition at -78^0 of 1 equivalent of trimethylaluminum in heptane and allowing the mixture to warm to -10^0 ($\sim$0.5 hr) afforded the lithium alanate reagent 6. To this reagent at -40^0 was added 1 equivalent of cyclopentenone 9[4] in ether (ether/hydrocarbon $\sim$1/1, v/v) and the 2-phase mixture was stirred at ambient temperatures for 16 hr. Protolytic work-up of the resulting single phase, followed by detritylation (80% acetic acid, 80^0, 0.5 hr)[5] and chromatography gave (71%) the methyl esters of *dl*-11-deoxy-PGE_1 (16) and its C-15 epimer (17) in a ratio of 44:56, respectively.



	X	R
1	I	H
2	I	$C(C_6H_5)_2(p\text{-}C_6H_4OCH_3)$
3	Li	$C(C_6H_5)_2(p\text{-}C_6H_4OCH_3)$
4	I	$C(C_6H_5)_3$
5	Li	$C(C_6H_5)_3$



	R
6	$C(C_6H_5)_2(p\text{-}C_6H_4OCH_3)$
7	$C(C_6H_5)_3$



8

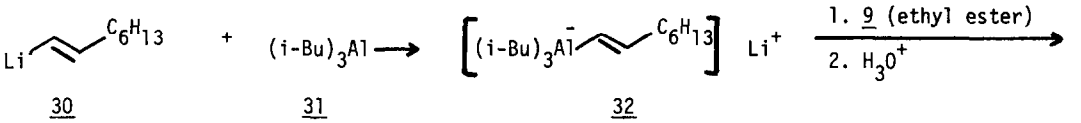
Additional examples of the use of this new lithium alanate procedure are given in Table I. Reaction of alanate reagents 7 and 8 with the various cyclopentenones,[6] each embracing features designed to inhibit β-oxidative fatty-acid metabolism, afforded the *dl*-11-deoxy-prostaglandins and their C-15 epimers, separated by dry-column chromatography upon silica gel. Products 18 thru 27, prepared with trimethylalanate 7, were obtained in a C-15-nat:C-15-epi ratio of approximately 45:55. In contrast, products 28 and 29, prepared via triisobutylalanate 8, were obtained in a ratio of 35:65 respectively.

TABLE I [7]

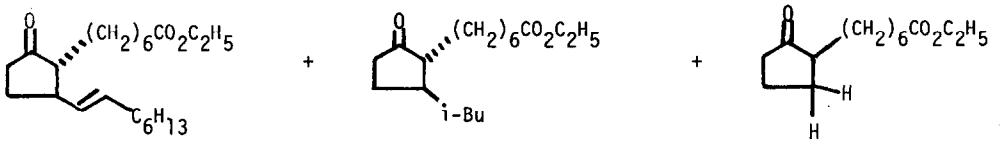
Starting ketone					*dl*-11-Deoxy-PGE[b]		*dl*-15-epi-11-Deoxy-PGE[b]	
	X	R	R'	Yield, %[a]				
9	CH_2	H	CH_3	53-71 (3 exp)	16	(83.5-85.0°)	17	(53-56°)
10	CH_2	CH_3	CH_3	43	18		19	
11	CH_2	C_2H_5	CH_3	51	20		21	
12	CH_2	C_6H_5	C_2H_5	24	22		23	
13	O	H	C_2H_5	38	24		25	
14	S	H	C_2H_5	27	26		27	
15	$C(CH_3)_2$	H	C_2H_5	47	28	(62-64°)	29	

[a]Total yields of the two epimeric products obtained after detritylation.
[b]Acids, obtained by saponification of the respective esters, were oils unless otherwise indicated.

Preliminary observations concerning the effects of solvent and alkyl ligands upon the reactivity of these alanate reagents are of interest. Solvent effects were studied with the reaction of cyclopentenone 9 (ethyl ester) and alanate reagent 32, prepared from E-1-octenyllithium (30) and triisobutylaluminum (31). The results, summarized in Table II, indicate that reaction in hydrocarbon solvent is non-selective, since the products reflect octenyl, isobutyl, and hydride 1,4-transfer. However, in ether solvent octenyl transfer dominates. Conjugate reduction is presumed to arise via hydrogen donation from the isobutyl moiety. A cyclopentenone-derived polymer is generally observed and in the more basic THF becomes significant. The rate of consumption of cyclopentenone was noted qualitatively to be in the order: hydrocarbon > ether > THF.



30 31 32



33 34 35

TABLE II

Solvent Effects

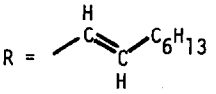
Solvent	E-1-Octenyl 1,4-Addition	Isobutyl 1,4-Addition	1,4-Reduction	Cyclopentenone Polymer
	33	34	35	
Hydrocarbon[a]	30%	11%	28%	11%
Hydrocarbon-ether (70:30, v/v)	59%	1-3%	8%	10-15%
Ether	64%	1-3%	6%	15%
THF	<50%	0	1-3%	~30%

[a]Hydrocarbon = toluene-hexane-heptane mixture

Alkyl-ligand effects were studied by reacting cyclopentenone 9 (ethyl ester) with alanate reagents prepared from E-1-octenyllithium (30) and trimethyl-, triethyl-, and triisobutylaluminum in ether-hydrocarbon solvent. These results are summarized in Table III. In general, methyl or isobutyl ligands are transferred to a lesser degree than ethyl. However, the isobutyl ligands also participate in conjugate reduction. Yields of alkenyl 1,4-addition appear to be greater with alanate reagents prepared via hydroalumination of 1-octyne.[2a]

TABLE III[a]

Lithium Alanate	1,4-Octenyl Transfer	1,4-Alkyl Transfer	Conjugate Reduction	Cyclopentenone Polymer
$[i\text{-}Bu_3\bar{A}l\text{-}R]Li^+$	59%	1-3%	8%	10-15%
$[Et_3\bar{A}l\text{-}R]Li^+$	21%	14%	0	10-15%
$[Me_3\bar{A}lR]Li^+$	50%	1-3%	0	28%
$[i\text{-}Bu_2MeAlR]Li^+$ [b]	70-80%	1-3%	3-10%	?



[a]Solvent: ether-hydrocarbon (~1:1, v/v)

[b]Prepared via hydroalumination of 1-octyne[2a]

REFERENCES

1. For the previous paper in this series, see: J. F. Poletto, K. F. Bernady, D. Kupfer, R. Partridge, and M. J. Weiss, J. Med. Chem., in press.

2. (a) K. F. Bernady and M. J. Weiss, Tetrahedron Lett., 4083 (1972); (b) M. B. Floyd and M. J. Weiss, Prostaglandins, 3, 921 (1973).

3. See (a) A. F. Kluge, K. G. Untch, and J. H. Fried, J. Amer. Chem. Soc., 94, 7827 (1972); (b) E. J. Corey and D. J. Beams, ibid., 94, 7210 (1972).

4. J. F. Bagli and T. Bogri, J. Org. Chem., 37, 2132 (1972).

5. These standard detritylation conditions are more vigorous than necessary for removal of the p-anisyldiphenylmethoxy group. For the ease of hydrolysis of p-anisyldiphenylmethyl ethers, see M. Smith, D. H. Rammler, I. H. Goldberg, and H. G. Khorana, J. Amer. Chem. Soc., 84, 430 (1962).

6. The synthesis of these cyclopentenones will be the subject of a forthcoming publication from these laboratories. See also, K. F. Bernady, J. F. Poletto, M. J. Weiss, U.S. Pat., 3,836,581 (Sept. 17, 1974).

7. All new products had analytical and/or spectral data consistent with their assigned structures.