

OXOKETENE DITHIOACETALS AS VERSATILE SYNTHONS FOR ALTERNATIVE 1,3 TO 1,11
CARBONYL TRANSPOSITIONS : A NEW POLYENE SYNTHESIS

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Abstract - A model strategy for 1,7 to 1,11 carbonyl transpositions involving 1,2 addition of sodium borohydride or Grignard reagents to polyenyl oxoketene dithioacetals **8** obtained by condensation of bis(methylthio)polyenals 1-3 with active methylene ketones, followed by borontrifluoride etherate catalyzed methanolysis of the resulting polyenyl carbinol acetals **9** to give 1,n transposed polyene esters **10** has been described.

Carbonyl transposition in a molecular framework is one of the useful transformations in organic synthesis¹. Despite the abundance of carbonyl functionality in organic molecules, its transpositions have not been fully exploited to realize many synthetic objectives through programmed studies. Among the possible variants, the 1,2-carbonyl transpositions have been by far the largest group of reactions described in the literature. The 1,3-carbonyl transpositions in α,β -unsaturated ketones, β -alkylthioenones and α -oxoketene dithioacetals and their variants are the next largest group of reactions described in the literature². However, only a limited number of examples involving 1,4-transfer of carbonyl group are available in the literature, while those involving 1,5- and 1,6-carbonyl group transpositions are generally confined to intramolecular hydride shift only¹. To our knowledge, the only example of intramolecular 1,7-carbonyl transposition available in the literature appears to be the conversion of 3,4-dehydro- β -ionone to megastigma-4,6,8-trien-1-one through a series of three [2,3] sigmatropic rearrangements of the intermediate allylic sulfoxide³. Recently Duhamel and co-workers have reported the reactions of functionalized silyloxy and alkoxy polyene lithium reagents with aldehydes or ketones followed by hydrolysis under mild reaction conditions to yield the corresponding polyenals which could be considered as examples of 1,5 and 1,7-carbonyl transpositions⁴. Therefore, there appears to be no examples beyond 1,7-carbonyl transpositions in the literature.

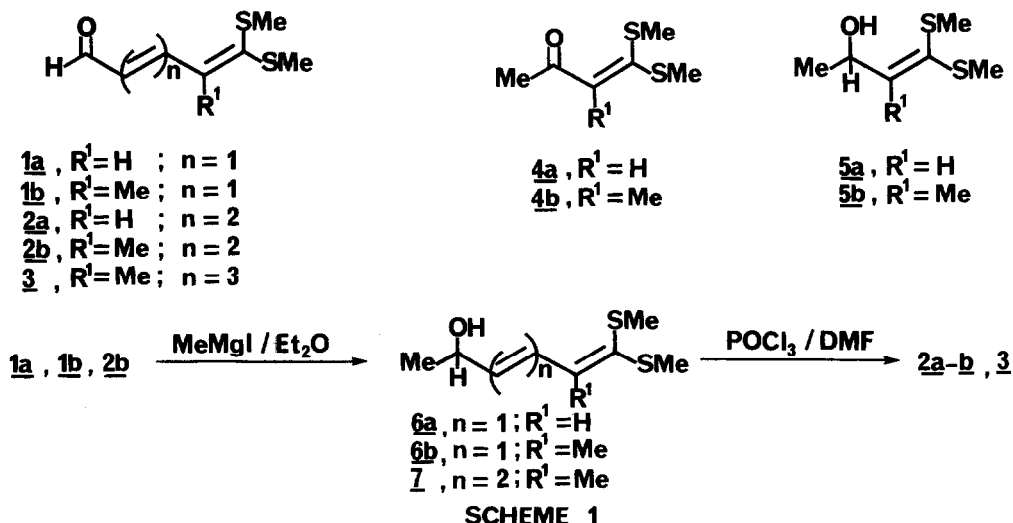
As a part of our continued interest in the chemistry of α -oxoketene dithioacetals, we have already reported the examples of 1,3-carbonyl transpositions involving these versatile intermediates⁵. The general methodology for these transformations involves 1,2-nucleophilic addition of sodium borohydride, Grignard and organolithium reagents to the α -oxoketene dithioacetals and subsequent methanolysis (or hydrolysis) of the allylic alcohols to α,β -unsaturated esters. We now wish to report successful application of higher vinylogous oxoketene dithioacetals to achieve 1,7, 1,9

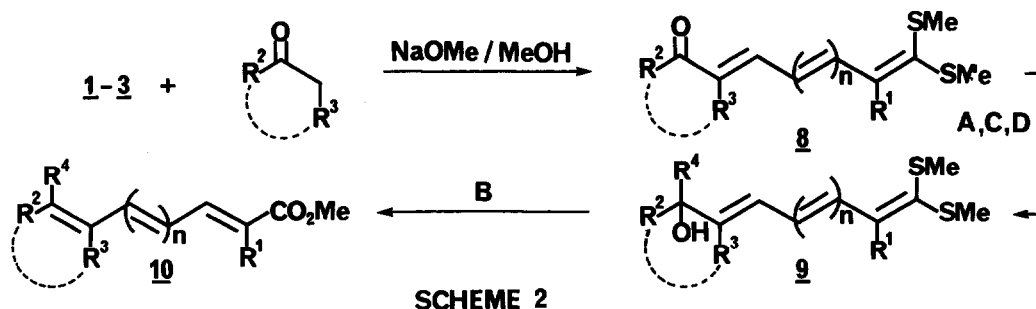
and 1,11 carbonyl transpositions which provide new routes to polyene ester synthesis. Our results are reported herein.

The basic strategy for the present methodology involves the condensation of the key bis(methylthio)polyenals 1-3 with active methylene ketones to afford the corresponding polyenyl oxoketene dithioacetals 8 (Scheme 1 and 2) and subject them to 1,2-reduction with sodium borohydride to yield the corresponding carbinols 9 followed by their BF_3 -etherate catalyzed methanolysis to the final 1,n transposed polyene esters 10. Alternatively, the polyenals 1-3 also serve as useful substrates for alkylative carbonyl transpositions by treatment with alkyl/aryl Grignard reagents followed by solvolysis to afford the corresponding polyene esters.

The hitherto unreported 1,5-pentadienals 1a-b were conveniently prepared in good yields by Vilsmeier-Haack formylation^{5f} of the carbinol acetals 5 obtained by 1,2-reduction of oxoketene dithioacetals 4. The corresponding heptatrienals 2a-b and the nonatetraenal 3 were similarly obtained from carbinols 6 and 7 respectively (Scheme 1). The all *trans* configuration around the double bonds in 1-3 was assigned on the basis of their ^1H NMR spectra⁶.

In a typical experiment, when the pentadienal 1a was condensed with acetophenone in the presence of sodium methoxide, the corresponding 7-bis(methylthio)-1-phenyl-2,4,5-heptatriene-1-one (8a)⁶ was obtained in 95% yield (Table). The other polyenones 8b-j⁶ were similarly obtained from the respective polyenals 1-3 and the appropriate active methylene ketones in 75-95% overall yields. The ketone 8a on reduction with borohydride, yielded the corresponding carbinol acetal 9a in nearly quantitative yield, which on BF_3 -etherate assisted methanolysis gave the expected 7-phenyl-2,4,6-heptatrienoate 10a⁶ in 80% yield through 1,7-carbonyl transposition (Table). The other enones 8b-c and 8g similarly afforded the corresponding 1,7-transposed triene esters 10b-c⁶ and 10g in overall high yields. (Table, entries 2,3, and 7). The tetraenones (8d-e and 8h) under similar reaction sequence underwent 1,9-carbonyl transposition to afford the corresponding



Table: Synthesis of Polyene esters 10 through 1,n Carbonyl Transpositions

Entry	Starting material	Reagent/conditions	Product	R ¹	R ²	R ³	R ⁴	n	1,n Transposition	%Yield ^a <u>10</u>
1	(<u>1a</u>)	<u>8a</u> A, B	<u>10a</u>	H	C ₆ H ₅	H	H	1	1, 7	80
2	(<u>1a</u>)	<u>8b</u> A, B	<u>10b</u>	H	2-Thienyl	H	H	1	1, 7	79
3	(<u>1a</u>)	<u>8c</u> A, B	<u>10c</u>	H	Me	H	H	1	1, 7	76
4	(<u>2a</u>)	<u>8d</u> A, B	<u>10d</u>	H	C ₆ H ₅	H	H	2	1, 9	70
5	(<u>2b</u>)	<u>8e</u> A, B	<u>10e</u>	Me	4-ClC ₆ H ₄	H	H	2	1, 9	70
6	(<u>3</u>)	<u>8f</u> A, B	<u>10f</u>	Me	C ₆ H ₅	H	H	3	1, 11	85
7	(<u>1a</u>)	<u>8g</u> A, B	<u>10g</u>	H	R = MeO	H	H	1	1, 7	76
8	(<u>2b</u>)	<u>8h</u> A, B	<u>10h</u>	Me	R = MeO	H	H	2	1, 9	80
9	(<u>3</u>)	<u>8i</u> A, B	<u>10i</u>	Me	R = MeO	H	H	3	1, 11	80
10	(<u>1b</u>)	<u>8j</u> C, B	<u>10j</u>	Me	R = H	Me	Me	1	1, 7	75
11	—	<u>1b</u> D, B	<u>10k</u>	Me	H	H	C ₆ H ₅	0	1, 5	85 ^b

λ = NaBH₄/EtOH/ Δ ; B = BF₃·Et₂O/MeOH/ Δ ; C = MeMgI/Et₂O; D = C₆H₅MgBr/Et₂O;
^ayields of pure 10a-j from 8a-j; ^byield of 10k from 1b.

tetraene esters (10d-e and 10h, entries 4,5 and 8)⁶ in 70-80% overall yields. Further, entries 6 and 9 represent the examples of reductive 1,11-carbonyl transposition to afford the corresponding polyene esters 10f⁶ and 10i⁶ in high yields under similar reaction conditions (Table). To illustrate an alkylative 1,7-carbonyl transposition, methylmagnesium iodide was added to the cyclic trienone 8j to yield the corresponding carbinol 9j, which under the described solvolytic conditions gave the corresponding 7-methyltriene ester 10j⁶ in 75% yield (entry 10). Similarly as an example of 1,5-carbonyl transposition, the 2-methyl-5-phenylpentadienoate 10k was obtained from 1b through 1,2-addition of phenylmagnesium bromide and subsequent methanolysis sequence (Table, entry 11).

In summary, a model strategy for alternative 1,3- to 1,11-carbonyl transpositions as useful synthetic tool for polyene esters through appropriately functionalized vinylogous oxoketene dithioacetals has been realized. The methodology holds considerable promise for the synthesis of natural products containing polyene structural features such as retinal and

other members of the family which is in progress. To the best of our knowledge this is the first report on 1,9-and 1,11-carbonyl transpositions.

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6. The structure of all the compounds were confirmed with the help of spectral and analytical data. The high resolution ^1H NMR spectra of trienones (8a-c, 8g) tetraenones (8d-e, 8h) and the corresponding polyene esters (10a-e, 10g-h) exhibited all *trans* stereochemistry, while it was not possible to make stereochemical assignment for the higher homologs (8f, 8i, 10f, 10i) on the basis of ^1H NMR spectral data. The spectral data for few compounds are given below:

7,7-Bis(methylthio)-2,4,6-heptatrienal (2a): viscous liquid; 56%; IR (neat) 1670, 1600 cm^{-1} ; ^1H NMR (CCl_4 , 90MHz) δ 2.31 (s, 3H, SMe); 2.32 (s, 3H, SMe); 6.01 (dd, J=16, 8, 1H, H-2); 6.29 (d, J=12, 1H, H-6); 6.33 (dd, J=16, 12, 1H, H-4); 6.93-7.38 (m, 2H, H-3, H-5); 9.52 (d, J=8, 1H, CHO); m/z 200 (M^+ , 76%).

9,9-Bis(methylthio)-8-methyl-2,4,6,8-nonatetraenal (3): yellow viscous liquid; 70%; IR (neat) 1675, 1612, 1585 cm^{-1} ; ^1H NMR (CCl_4 , 90MHz) δ 2.11 (s, 3H, Me); 2.24 (s, 3H, SMe); 2.34 (s, 3H, SMe); 6.01 (dd, J=15, 8, 1H, H-2); 6.20-6.85 (m, 3H, olefinic); 7.03 (dd, J=15, 12, 1H, H-5); 7.43 (d, J=15, 1H, H-7); 9.49 (d, J=8, 1H, CHO); m/z 240 (M^+ , 100%).

7,7-Bis(methylthio)-1-phenyl-2,4,6-heptatriene-1-one (8a): red crystals; 95%; m.p. 62°C; IR (KBr) 1643, 1590 cm^{-1} ; ^1H NMR (CDCl_3 , 300MHz) δ 2.38 (s, 3H, SMe); 2.39 (s, 3H, SMe); 6.36 (d, J=11, H-6); 6.45 (dd, J=15, 11, 1H, H-4); 6.96 (d, J=16, 1H, H-2); 7.26 (dd, J=15, 11, 1H, H-5); 7.43-7.57 (m, 4H, arom+H-3); 7.92-7.94 (m, 2H, arom); m/z 276 (M^+ , 10%); 213 (70%).

9,9-Bis(methylthio)-8-methyl-1-(4-chlorophenyl)-2,4,6,8-nonatetraene-1-one (8e): red crystals; 75%; mp 120-121°C; IR (KBr) 1642, 1597 cm^{-1} ; ^1H NMR (CCl_4 , 300MHz) δ 2.17 (s, 3H, Me); 2.29 (s, 3H, SMe); 2.38 (s, 3H, SMe); 6.45 (dd, J=15, 11, 1H, H-6); 6.52 (dd, J=15, 11, 1H, H-4); 6.84 (dd, J=15, 11, 1H, H-5); 6.93 (d, J=15, 1H, H-2); 7.42-7.56 (m, 4H, arom+H-7, H-3); 7.87-7.90 (m, 2H, arom); m/z 350 (M^+ , 25%); 352 (11%).

2-[1,1-Bis(methylthio)-2-methyl-1,3,5,7-nonatetraenylidene]-6-methoxy-1-tetralone (8i): deep red semisolid; 95%; IR (neat) 1650, 1610 cm^{-1} ; ^1H NMR (CCl_4 , 300 MHz) δ 1.96 (s, 3H, Me); 2.10 (s, 3H, SMe); 2.23 (s, 3H, SMe); 2.73 (s, 4H, CH_2); 3.66 (s, 3H, OMe); 6.10-6.85 (m, 6H, arom+olefinic); 7.15-7.49 (m, 3H, olefinic); 7.93 (d, J=8, 1H, arom); m/z 398 (M^+ , 20%); 351 (23%).

Methyl 9-phenyl-2,4,6,8-nonatetraenoate (10d): yellow crystals; 70%; m.p. 152-153°C; IR (KBr) 1708, 1618 cm^{-1} ; ^1H NMR (CDCl_3 , 90MHz) δ 3.81 (s, 3H, OMe); 5.89 (d, J=15, 1H, H-2); 6.22-6.89 (m, 6H, olefinic); 7.02-7.25 (m, 6H, arom+H-3); m/z 240 (M^+ , 94%).

Methyl 2-methyl-11-phenyl-2,4,6,8,10-undecapentaenoate (10f): yellow crystals; 85%; m.p. 142-143°C; IR (KBr) 1705, 1617 cm^{-1} ; ^1H NMR (CDCl_3 , 90 MHz) δ 2.00 (s, 3H, Me); 3.63 (s, 3H, OMe); 6.30-7.10 (m, 7H, olefinic); 7.10-7.85 (m, 7H, arom+olefinic); m/z 280 (M^+ , 68%); 149 (100%).