Acetogenin Synthesis. Organocopper Reagents, Anions of 1,3-Dithians and of Protected Cyanohydrins as Intermediates in Ketide Side-chain Synthesis

By **Lino Colombo, Cesare Gennari, Marco Santandrea, Enrica Narisano,** and **Carlo Scolastico,*** Istituto di Chimica Organica dell'Università, Centro C.N.R. per le Sostanze Organiche Naturali, via Saldini 50, 20133 Milano, Italy

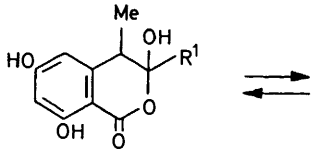
The synthesis is reported of 3-s-butyl-4-methyl-3,6,8-trihydroxy-3,4-dihydroisocoumarin (1a) and 3-(1-methylprop-1-enyl)-4-methyl-3,6,8-trihydroxy-3,4-dihydroisocoumarin (1b) using organocopper reagents and anions of 1,3-dithians for compound (1a), and anions of 1,3-dithians and of *O*-trimethylsilylcyanohydrins for compound (1b). The synthetic methods used represent new means for attaining an extensive range of acetogenins of natural origin and of biogenetic intermediates.

THE development of synthetic methods for natural systems of polyketide origin poses the problem of obtaining ketones of the type $Ar–CHR^1–CO–CHR^1R^2$ and $Ar–CHR^1–CO–CR^1{=}CHR^2$ (R^1 = H, Me; R^2 = alkyl). For the first series of compounds the general synthetic method used hitherto was the condensation between the appropriate phenylacetyl chloride and a Grignard reagent, in the presence of iron(III) chloride [in the case of (±)-ascochitine [1] and tetrahydrosclerotiorin [2]] or cadmium chloride (as in the case of tetrahydrosclerotoquinone [2]). On the other hand, α,β-unsaturated carbonyl derivatives have been synthesized according to a method which had, as the key step, the Darzens condensation between an aromatic aldehyde and α-bromo-γ-valerolactone,[3] or the reaction between a diazoalkane and the appropriate phenylacetyl chloride [as reported for (±)-sclerotiorin [4] and (±)-mitorubrin [5]].

We effected the synthesis of (1a) and (1b), possible biogenetic intermediates of cochlioquinones [6] and stemphone,[7] by the action of organocopper compounds [8] on 3,5-dimethoxyphenylacetyl chloride, or condensing benzyl bromides with masked acyl anions [9] such as lithium dithians and protected lithium cyanohydrins. The best selection among each of these three general methods was made, taking into account the functional groups present on the aromatic ring, and also the presence of the conjugated double bond in the side-chain.

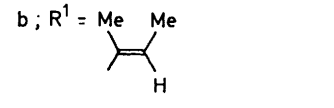
RESULTS AND DISCUSSION

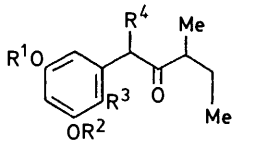
Synthesis of the lactol (1a) can be carried out by allowing 3,5-dimethoxyphenylacetyl chloride to react with s-butylmagnesium bromide in the presence of copper(I) bromide. The resulting ketone (3a) can be methylated in quantitative yield, in the benzyl position, with methyl iodide under phase-transfer conditions, to give (3b). This methylation, because of its simplicity, high yield, and the required stoicheiometric quantity of methyl iodide, could prove useful to introduce labelling. Demethylation with hydrobromic acid in the presence of tributylhexadecylphosphonium bromide, followed by formylation with triethyl orthoformate, led to the aldehyde (3c). The oxidation of the formyl group of (3c) has not hitherto been achieved, and was found to be complex; the methods based on the use of silver oxide in alkaline solution, manganese dioxide in n-hexane or chloroform, Collins' reagent, and potassium permanganate were quite ineffective. Appreciable yields were obtained only by use of the Corey method,[10] based on the use of sodium cyanide and manganese dioxide. In this specific case, however, the reaction only reaches the ketonitryl (3d) stage (70%); this compound can then be hydrolysed to the lactol (1a) with alkalis (85%).



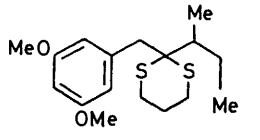
(1) (2)

a ; R^1 = Bu^s
b ; R^1 = Me Me



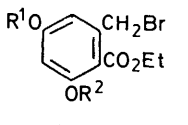


(3)



(4)

a ; $R^1 = R^2$ = Me ; $R^3 = R^4$ = H
b ; $R^1 = R^2 = R^4$ = Me ; R^3 = H
c ; $R^1 = R^2$ = H ; R^3 = CHO ; R^4 = Me
d ; $R^1 = R^2$ = H ; R^3 = COCN ; R^4 = Me
e ; $R^1 = R^2$ = H ; $R^3 = CO_2Me$; R^4 = Me



(5)

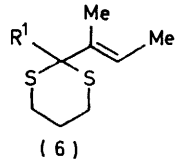
a ; R^1 = Me ; R^2 = H
b ; R^1 = Me ; R^2 = MEM
c ; $R^1 = R^2$ = H
d ; $R^1 = R^2$ = MEM

MEM = β-methoxyethoxymethyl

However, this oxidation can be more easily performed with sodium chlorite and sulphamic acid [11] (90%). Lactol (1a) has the same physicochemical characteristics as analogous compounds; [12] specifically, the two forms [ketoacid (2a) and lactol (1a)] can be observed in the mass spectrum. Compound (1a), by treatment with diazomethane, led to the formation of the methyl ester (3e). The synthesis of (1a) can be markedly simplified by condensing 2-lithio-2-s-butyl-1,3-dithian with 3,5-dimethoxybenzyl bromide. This method, besides preventing the homologation reaction (from 3,5-dimethoxybenzoic acid into 3,5-dimethoxyphenylacetic acid) makes it possible to obtain the carbonyl group already protected. At this stage, the protection of the carbonyl group permits further changes in the molecule, such as metallation in the 4-position of the ring in order to provide carboxylated or alkylated products. The dithian (4) can be converted into its related ketone (3a) in high yield using methyl fluorosulphonate.[13]

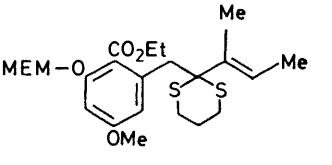
In the synthesis of the lactol (1b), the presence of the double bond makes the formylation and oxidation reactions extremely critical; therefore it is necessary to start from a benzyl halide which already has an ethoxycarbonyl group. The phenol (5a) was converted into its related ether (5b) by treatment with sodium hydride and β-methoxyethoxymethyl (MEM) chloride; [14] compound (5b), without purification, underwent condensation with lithiodithian (6a), obtained by metallation of dithian (6b). The resulting unsaturated dithian (7) was hydrolysed into (8a) in appreciable yields (25%) only through the use of *O*-mesitylenesulphonylhydroxylamine; [15] other dethioketalization reagents (methyl iodide, mercuric chloride, cerium ammonium nitrate, methyl fluorosulphonate, *N*-bromosuccinimide, and chloramine T) were ineffective. The treatment of ketone (8a) with methyl iodide, under the same conditions used in the case of (3a), provided (8b). This compound can be converted into the lactol (1b) with lithium iodide and collidine, unfortunately in low yield (5%).* In order to overcome the problems involved in this synthesis, such as dithian removal and phenol demasking, lithio-*O*-trimethylsilylcyanohydrin (9a) and di-MEM ether (5d) should preferably be used. The protective group of phenol (5c) was chosen because it is easily removed under mild conditions which preserve the double-bond geometry. The condensation of (5d) with (9a) led to a good yield of (10). Treatment of (10) with tetraethylammonium fluoride produced the ketone (8c) (95%), which was converted into (8d) by methylation under the above-mentioned phase-transfer conditions, and subsequently hydrolysed to give (8e). Alkaline hydrolysis led to the final product (1b). Analysis of these synthetic methods leads to the conclusion that the use of lithiodithians is most suitable for ketones of type (3), which have a saturated side chain.

The rapidity of the method, the high reactivity of benzyl bromides, the simplicity of the preparation of alkyl dithians, and the subsequent facile removal of the masking group, makes this method preferable to using organocopper and organocadmium compounds. On the other hand, the alkylation of lithio-*O*-trimethylsilylcyanohydrins with benzyl bromides is optimal for obtaining unsaturated ketones of type (8).

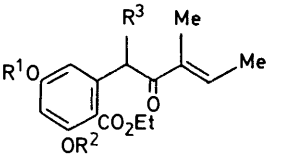


(6)

a ; R^1 = Li
b ; R^1 = H

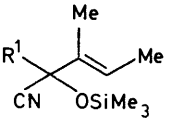


(7)



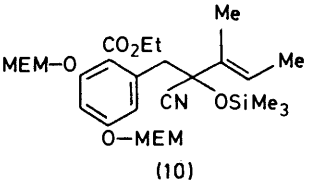
(8)

a; R^1 = Me; R^2 = MEM; R^3 = H
b; R^1 = Me; R^2 = MEM; R^3 = Me
c; R^1 = R^2 = MEM; R^3 = H
d; R^1 = R^2 = MEM; R^3 = Me
e; R^1 = R^2 = H; R^3 = Me



(9)

a ; R^1 = Li
b ; R^1 = H



(10)

MEM = β—methoxyethoxymethyl

EXPERIMENTAL

Reactions using organolithium compounds were carried out in an inert atmosphere (purified argon). Mass spectra were recorded with a Varian MAT 112 spectrometer, i.r. spectra with a Perkin-Elmer 257 spectrophotometer, and n.m.r. spectra with Varian A-60 (60 MHz) or XL-100 (100 MHz) instruments. Kieselgel 60 F_{254} (Merck) was used for t.l.c.; 70—230 mesh silica gel (Merck) and 60—100 mesh Florisil (B.D.H.) were used for column chromatography.

Physical and spectroscopic data for compounds (1a), (4), (7), (8b), (5c), (10), (8d), (8e), and (1b) are in the Table. Corresponding data for compounds (3a—e), (6b), (8a), and (9b) are deposited as Supplementary Publication No. SUP 22613 (3 pp.).†

1-(3,5-*Dimethoxyphenyl*)-3-*methylpentan*-2-*one* (3a).—The Grignard reagent prepared from 2-bromobutane (49.2 g) and magnesium (8.58 g) in ether (270 ml) was added (with stirring) to a solution of 2-(3,5-dimethoxyphenyl)acetyl chloride [prepared from the acid (30 g) and oxalyl chloride in benzene] in ether (120 ml) containing CuBr (43 g) at

* Other methods (BBr_3, $SiMe_3I$) were ineffective.

† For details see Notice to Authors No. 7, *J.C.S. Perkin I*, 1978, Index issue.

Physical data

Compd.	M.p. (°C) (solvent)	$\nu_{max.}$ [a]/cm^{-1}	^{1}H N.m.r.	*m/e* (%)	Formula	Found (%) [Reqd. (%)] C	H
(1a)	125—127 (Et_2O–n-*Hexane*)	3 400, 3 240 (OH), 1 665 (C=O) [b]	(C_5D_5N) 11.95 (1 H, s, OH), 6.75 (1 H, d, ArH), 6.65 (1 H, d, ArH), 4.77 (1 H, s, OH), 4.07 (1 H, q, ArCHMe, *J* 7 Hz), 2.18—2.70 [1 H, m, C*H*(Et)Me], 1.48 (3 H, d, ArCH*Me*, *J* 7 Hz), 1.03 [3 H, d, *Me*CHC(OH), *J* 7 Hz], 0.86 (3 H, t, *Me*CH_2, *J* 8 Hz)	266 (*M*$^+$, 4), 209 (9), 191 (14), 164 (93)	$C_{14}H_{18}O_5$	62.97 [63.14	6.80 6.81]
(4)	56—58 (MeOH–H_2O)		($CDCl_3$) 6.56 (2 H, d, ArH, J_m 3 Hz), 6.34 (1 H, t, ArH, J_m 3 Hz), 3.75 (6 H, s, OMe), 3.20 (2 H, s, $ArCH_2$), 2.64—2.93 (4 H, m, CH_2S), 1.13 (3 H, d, MeCH, *J* 7 Hz)	326 (*M*$^+$, 2), 269 (27), 219 (10), 195 (22), 175 (60), 151 (100)	$C_{17}H_{26}O_2S_2$	62.48 [62.56	8.00 8.03]
(7)	Oil	1 720 (C=O) [c]	($CDCl_3$) 6.65 (1 H, d, ArH, J_m 2.5 Hz), 6.59 (1 H, d, ArH, J_m 2.5 Hz), 6.00 (1 H, m, C=CH), 5.19 (2 H, s, OCH_2O), 4.33 (2 H, q, CO_2CH_2, *J* 7 Hz), 3.73 (3 H, s, ArOMe), 4.30—3.80 (4 H, m, OCH_2-CH_2O), 3.33 (3 H, s, OMe), 3.27 (2 H, s, $ArCH_2$), 2.55—2.75 (4 H, m, CH_2S), 1.80—2.00 (2 H, m, CH_2), 1.60—1.80 (6 H, m, MeC=CMe), 1.35 (3 H, t, CO_2CH_2Me, *J* 7 Hz)		$C_{23}H_{34}O_6S_2$		
(8b)	Oil	1 720—1 675 (C=O)	($CDCl_3$) 6.50—6.90 (1 H, m, C=CH), 6.62 (1 H, d, ArH), 6.28 (1 H, d, ArH), 5.25 (2 H, s, OCH_2O), 4.45 (1 H, q, ArCH, *J* 7 Hz), 4.38 (2 H, q, CO_2CH_2), 3.40—3.90 (4 H, m, OCH_2CH_2O), 3.71 (3 H, s, ArOMe), 3.34 (3 H, s, OMe), 1.68—1.85 (6 H, m, MeC=CMe), 1.34 (3 H, d, ArCH*Me*, *J* 7 Hz), 1.36 (3 H, t, CO_2CH_2Me)		$C_{21}H_{30}O_7$		
(5c)	121—122 ($CHCl_3$)	3 600, 3 270 (OH) 1 655 (C=O)	[$(CD_3)_2SO$] 6.52 (1 H, d, ArH), 6.37 (1 H, d, ArH), 4.60 (2 H, s, $ArCH_2Br$), 4.37 (2 H, q, CO_2CH_2), 1.37 (3 H, t, CO_2CH_2Me)	276 (39), 274 (40), 230 (78), 228 (79), 195 (50), 167 (90), 149 (90), 69 (100)	$C_{10}H_{11}BrO_4$	43.65 [43.63	4.00 4.00]
(10)	Oil	1 720 (C=O)	($CDCl_3$) 6.82—6.93 (2 H, m, ArH), 5.60—6.20 (1 H, m, C=CH), 5.28 (2 H, s, OCH_2O), 5.32 (2 H, s, OCH_2O), 4.37 (2 H, q, CO_2CH_2), 3.63 (2 H, s, $ArCH_2$), 3.30—4.00 (8 H, m, OCH_2CH_2O), 3.38 (6 H, s, OMe), 1.53—1.88 (6 H, m, MeC=CMe), 1.35 (3 H, t, CO_2CH_2Me), 0.20 (9 H, s, $SiMe_3$)		$C_{27}H_{43}NO_9Si$		
(8d)	Oil	1 715, 1 675 (C=O)	($CDCl_3$) 6.63—6.82 (1 H, m, C=CH), 6.73 (1 H, d, ArH), 6.38 (1 H, d, ArH), 5.18 (2 H, s, OCH_2O), 5.14 (2 H, s, OCH_2O), 4.42 (1 H, q, ArCH, *J* 7 Hz), 4.35 (2 H, q, CO_2CH_2), 3.40—3.90 (8 H, m, OCH_2CH_2O), 3.32 (6 H, s, OMe), 1.60—1.83 (6 H, m, MeC=CMe), 1.33 (3 H, t, CO_2CH_2Me), 1.30 (3 H, d, ArCH*Me*, *J* 7 Hz)		$C_{24}H_{36}O_9$		
(8e)	Amorphous	3 580, 3 240 (OH), 1 675, 1 655 (C=O)	($CDCl_3$) 6.50—6.75 (1 H, m, CH=C), 6.42 (1 H, d, ArH), 6.22 (1 H, d, ArH), 5.30 (1 H, q, ArCH, *J* 7 Hz), 4.48 (2 H, q, CO_2CH_2), 1.64—1.82 (6 H, m, *Me*C=CMe), 1.33 (3 H, t, CO_2CH_2Me), 1.31 (3 H, d, ArCHMe, *J* 7 Hz),	292 (*M*$^+$, 6), 246 (31), 164 (8), 149 (5), 264 (7), 83 (100)	$C_{16}H_{20}O_5$		
(1b)	Amorphous	3 560, 3 240 (OH), 1 665 (C=O)	($CDCl_3$) 6.47 (1 H, d, ArH), 6.29 (1 H, d, ArH), 5.70—6.20 (1 H, m, CH=C), 3.58 (1 H, q, ArCH, *J* 6.5 Hz), 1.56—1.78 (6 H, m, MeC=CMe), 1.28 (3 H, d, ArCH*Me*, *J* 6.5 Hz)	264 (*M*$^+$, 12), 180 (19), 179 (100), 164 (9), 149 (22)	$C_{14}H_{16}O_5$		

[a] Solution in $CHCl_3$ unless stated otherwise. [b] KBr disc. [c] Liquid film.

—50 °C. The temperature was slowly raised to 25 °C and the product was isolated in the normal manner to yield the ketone (3a) (25 g, 70%).

2-(2-*Formyl*-3,5-*dihydroxyphenyl*)-4-*methylhexan*-3-*one* (3c).—A solution of (3a) (6.8 g) in CH_2Cl_2 (32 ml) was treated with tetrabutylammonium hydroxide (40% in water, 30.1 g), water (32 ml), and CH_3I (2.7 ml). The mixture was stirred at 45 °C for 2 h. The organic phase was evaporated, and the residue taken up in ether and filtered from tetrabutylammonium iodide, giving (3b) (6.84 g,

95%). Demethylation of the foregoing methoxy-ketone (1.15 g) occurred during 6 h in a boiling mixture of 48% hydrobromic acid (5 ml) and tributylhexadecylphosphonium bromide (0.39 g) (under nitrogen) to yield 2-(3,5-*dihydroxyphenyl*)-4-*methylhexan*-3-*one* (0.87 g, 85%). A solution of this phenol (0.86 g) in triethyl orthoformate (17 ml) was treated with hydrogen chloride for 15 min at 0 °C and the precipitate was collected. Purification (from ether) gave 6,8-*dihydroxy*-4-*methyl*-3-*s*-*butyl*-2-*benzopyrylium chloride*. It was dissolved in 5% aqueous NaOH, and the cooled mixture was then acidified with 12% aqueous HCl and extracted with ether. The organic extract was dried (Na_2SO_4) and evaporated to give the aldehyde (3c) (0.67 g, 69%).

Oxidation of (3c).—(i) *With Corey's method.* A solution of (3c) (0.048 g) in methanol (5 ml) was treated with NaCN (0.066 g), acetic acid (0.050 ml), and freshly prepared MnO_2 (0.673 g), and the mixture was stirred at 55—60 °C for 6 h. The solvent was then evaporated off and the residue was taken up in ether, washed with saturated brine, dried (Na_2SO_4), evaporated, and the crude product was chromatographed on silica gel. Elution with n-hexane–ether gave the ketonitryl (3d) (0.037 g, 70%). Hydrolysis of this compound (0.097 g) occurred during 40 min with a boiling solution of 0.02N-NaOH (70 ml) to give the lactol (1a) (0.080 g, 86%).

(ii) *With* $NaClO_2$–NH_2SO_3H. A mixture of the aldehyde (3c) (0.16 g) in water (30 ml) and acetone (5 ml) was treated with NH_2SO_3H (0.09 g) and 85% $NaClO_2$ (0.095 g), and after 2 h at room temperature the resulting solution was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and evaporated, giving the lactol (1a) (0.15 g, 90%).

2-(2-*Methoxycarbonyl*-3,5-*dihydroxyphenyl*)-4-*methylhexan*-3-*one* (3e).—A solution of the lactol (1a) (0.12 g) in ether (5 ml) was treated with CH_2N_2 at 0 °C. The reaction mixture was then evaporated *in vacuo*, giving (3e) (0.12 g, 95%).

2-(3,5-*Dimethoxyphenylmethyl*)-2-*s*-*butyl*-1,3-*dithian* (4).—A solution of 2-s-butyl-1,3-dithian (7.14 g) in THF (120 ml) at −40 °C was treated with 1.5N-n-butyl-lithium in n-hexane (19.8 ml). The mixture was stirred at −15 °C for 2 h. To the resulting solution, cooled to −78 °C, was added 3,5-dimethoxybenzyl bromide (6.25 g) in THF (120 ml). After 1 h at −78 °C, the mixture was treated with saturated brine, and the aqueous phase was extracted with ether. The organic extract was dried (K_2CO_3), evaporated, and the crude mixture was chromatographed on silica gel (n-hexane–ethyl ether) to give compound (4) (6.6 g, 75%).

Hydrolysis of the Dithian (4).—A solution of (4) (2.2 g) in CH_2Cl_2 (70 ml) was treated under nitrogen at 0 °C with CH_3OSO_2F (0.82 ml), and the mixture was stirred at 0 °C for 10 min, and then at room temperature for 3 h. The work-up was accomplished by quenching with 3% aqueous $CuSO_4$ and extraction with CH_2Cl_2. The extracts were dried (Na_2SO_4), evaporated, and the crude product was chromatographed on silica gel (n-hexane–ether) to give the ketone (3a) (1.43 g, 90%).

Ethyl 2-(β-*Methoxyethoxymethoxy*)-4-*methoxy*-6-*bromomethylbenzoate* (5b).—A solution of (5a) [16] (0.145 g) in dry THF (5 ml) was treated under nitrogen at −10 °C with NaH (0.05 g, 50% oil). The mixture was stirred for 30 min, cooled to −20 °C, and treated with MEM chloride [14] (0.08 ml). After 15 h at −20 °C the mixture was treated with saturated brine, and the aqueous phase was extracted with ether. The organic extracts were dried (K_2CO_3) and evaporated. The product is unstable and can be stored at −25 °C only for a few hours.

2-[2-*Ethoxycarbonyl*-3-(β-*methoxyethoxymethoxy*)-5-*methoxyphenylmethyl*]-2-(E-1-*methylprop*-1-*enyl*)-1,3-*dithian* (7).—A solution of (6b) (0.56 g) [prepared from (2*E*)-2-methylbut-2-enal [17] and propanedithiol with BF_3–ether] in THF (6 ml) at −78 °C was treated with 1.6N-n-butyl-lithium in n-hexane (2 ml). The mixture was stirred at −20 °C for 3 h. The solution, cooled to −78 °C, was treated with a solution of (5b) (0.76 g) in THF (4 ml). After a few minutes the reaction mixture was worked up as for (4) giving (7) (0.8 g, 85%).

(3E)-1-[2-*Ethoxycarbonyl*-3-(β-*methoxyethoxymethoxy*)-5-*methoxyphenyl*]-3-*methylpent*-3-*en*-2-*one* (8a).—A solution of (7) (0.47 g) in CH_2Cl_2 (7 ml) at 0 °C was treated with a mixture of *O*-mesitylenesulphonylhydroxylamine (1 g, water 30%) in CH_2Cl_2 (7 ml). The reagent should be freshly prepared [15] and the pH should exceed 3.5. The mixture was stirred at room temperature. T.l.c. [benzene–ethyl ether (6 : 4)] showed the disappearance of the starting product. The mixture was treated with ether (30 ml), filtered from ammonium mesitylenesulphonate, washed with saturated brine, dried (Na_2SO_4), and evaporated. The crude product was chromatographed ($CHCl_3$) on silica gel to give (8a) (0.095 g, 25%).

(4E)-2-[2-*Ethoxycarbonyl*-3-(β-*methoxyethoxymethoxy*)-5-*methoxyphenyl*]-4-*methylhex*-4-*en*-3-*one* (8b).—A solution of (8a) (0.12 g) in CH_2Cl_2 (0.7 ml) was treated with tetrabutylammonium hydroxide (40% in water, 0.29 g), water (0.25 ml), and CH_3I (0.029 ml) as described for compound (3a). Work-up as before yielded (8b) (0.108 g, 87%).

Deprotection of (8b).—A solution of (8b) (0.45 g) in anhydrous collidine (10 ml) was treated under nitrogen with anhydrous lithium iodide (1 g). The mixture was stirred and heated at reflux (180 °C) for 3 h. After cooling the mixture was diluted with ether, and washed with 1N-HCl, and water. The organic phase was dried (Na_2SO_4), evaporated, and preparative t.l.c. of the crude mixture with n-hexane–ethyl acetate (8 : 2) as developing agent provided the lactol (1b) (0.015 g, 5%).

Ethyl 2,4-*Bis*-(β-*methoxyethoxymethoxy*)-6-*bromomethylbenzoate* (5d).—A solution of (5a) [16] (1.76 g) in CH_2Cl_2 (40 ml) at −78 °C was treated with BBr_3 (1.73 ml). The temperature was slowly raised to 0 °C and the reaction mixture was stirred at this temperature for 15 h. The work-up was accomplished by quenching with water and extraction with ethyl acetate. The extracts were dried (Na_2SO_4), evaporated, and the crude product was chromatographed on silica gel. Elution with chloroform gave *ethyl* 2,4-*dihydroxy*-6-*bromomethylbenzoate* (5c) (0.920 g, 55%). A solution of this compound (0.41 g) in anhydrous THF (15 ml) was treated under nitrogen at −15 °C with MEM chloride [14] (0.38 ml) and NaH (0.29 g, 50% oil). The mixture was stirred for 15 h and worked up as for compound (5b), giving (5d) (0.538 g, 80%).

(3E)-2-*Cyano*-1-[2-*ethoxycarbonyl*-3,5-*bis*-(β-*methoxyethoxymethoxy*)*phenyl*]-3-*methyl*-2-*trimethylsilyloxypent*-3-*ene* (10).—A solution of di-isopropylamine (0.156 ml) in dry DME (1 ml) was treated at 0 °C with 2N-n-butyl-lithium in n-hexane (0.6 ml). After 30 min the resulting solution, cooled to −78 °C, was treated with (9b) (0.183 g) [prepared from (2*E*)-2-methylbut-2-enal [17] and trimethylsilyl cyanide with ZnI_2]. After 30 min, to the resulting solution was added compound (5d) (0.361 g) in DME (0.5 ml). After a

few min the reaction mixture was worked up as usual giving (10) (0.389 g, 88%).

2-[2-*Ethoxycarbonyl*-3,5-*bis*-(β-*methoxyethoxymethoxy*)-*phenyl*]-4(E)-4-*methylhex*-4-*en*-3-*one* (8d).—A solution of (10) (0.1 g) in THF (1 ml) was treated at room temperature with tetraethylammonium fluoride (0.1 g, water 30%). After 30 min the solvent was distilled off under reduced pressure and the residue was taken up in ether, washed with 5% aqueous NaOH, dried (K_2CO_3), and evaporated. The crude product was methylated as described for compound (3a). Column chromatography (Florisil, n-hexane–ethyl acetate) gave pure (8d) (0.088 g, 85%).

Lactol (1b).—A solution of (8d) (0.1 g) in THF (3 ml) was treated with 1N-HCl (1 ml). The mixture was stirred at 50 °C for 1 h, then diluted with saturated brine, and the mixture was extracted with ether. The organic extracts were dried (Na_2SO_4), evaporated, and the crude product was treated with a 0.02N-NaOH solution (35 ml) and then left at room temperature overnight. After cooling to 0 °C the mixture was acidified with 12% aqueous HCl (pH 2), extracted with ether, and the organic extracts were dried (Na_2SO_4) and evaporated. The crude product was chromatographed on silica gel; elution with n-hexane–ethyl acetate gave lactol (1b) (0.033 g, 82%).

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