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INVESTIGATIONS FOR SYNTHESIZING CHLOROTHRICOLIDE [1)]

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Abstract: *Functionally substituted acrylates 8a,b obtained by direct lithiation of the corresponding acids, and cyclohexanone derivative 6 accessible in a five step sequence afforded spirotetronates 9a,b containing the carbon skeleton and the stereochemistry of the top half of chlorothricolide 1 (R = H). Subsequent direct lithiation of the tetronate moiety in a-position enabled the introduction of the required a-hydroxy group.*

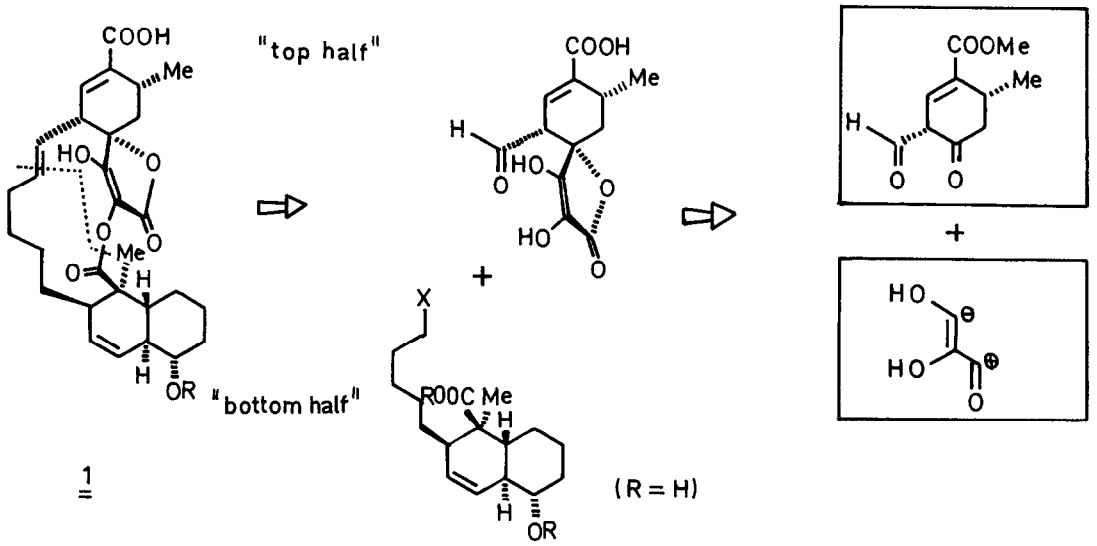
Recent interest in the synthesis of the macrolide antibiotic chlorothricin, which is active against Gram positive bacteria by inhibiting the reaction catalyzed by pyruvate carboxylase, resulted in approaches to the synthesis of the "top half" and the "bottom half" of the aglycon chlorothricolide 1 (Scheme 1) [2-4)]. The aglycon contains part of the activity of the antibiotic [2a,5)].

Inspection of the "top half" of this molecule may lead to a retrosynthetic analysis with a substituted cyclohexenone and a 1.3-dipolar species easily accessible from functionally substituted vinyl carbanions as synthetic equivalent (Scheme 1) [6)]. In this paper we are demonstrating the efficiency of this methodology [7)].

The cis-geometry required for the methyl and formyl group in the cyclohexenone moiety can be generated by a Diels-Alder reaction (Scheme 2 [8)]). For this aim pentenone 2 was transformed in a three step sequence to the electron rich butadiene derivative 3 with a protected formyl group and a methyl group in 1,4-position. Cycloaddition with methyl propiolate gave the cyclohexadiene derivative 4 in 73 % yield; however, liberation of the cyclohexenone moiety with tetrabutylammonium fluoride (TBAF) led not unexpectedly to elimination and concomitant loss of the cis relationship giving compound 7.

Therefore acrylate addition was carried out (yield 70 %). After desilylation of the reaction mixture with TBAF (84 %) the product with the carboxylate group in 4-position [9)] was obtained by crystallisation. It consisted of a 1:1-mixture of the cis and trans isomer (6-cis and 6-trans), which could be separated by column chromatography (silica gel, petroleum ether/ethyl acetate = 2:3). Ketalisation of the mixture of 6-cis and 6-trans with ethylene glycol in the

Scheme 1

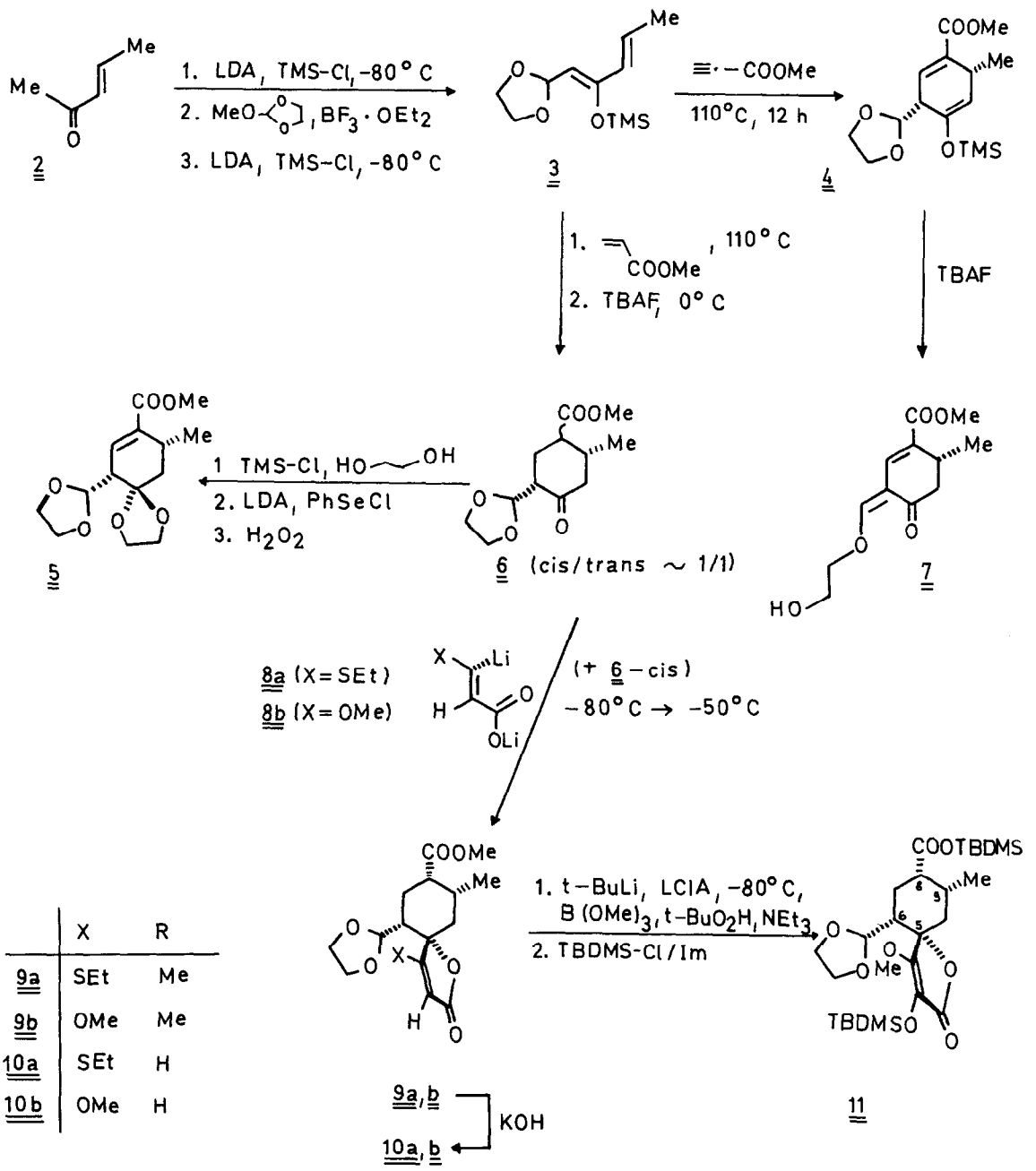


presence of chlorotrimethylsilane [10] and introduction of the double bond with lithium diisopropylamide (LDA)/phenylselenylyl chloride and hydrogen peroxide [11] afforded cyclohexenone derivative 5 in 74 % overall yield, demonstrating the expected ease of olefin formation at a later stage of the total synthesis of 1.

Both cyclohexanone derivatives 6-cis and 6-trans were successfully applied as electrophilic-nucleophilic species in one step tetronate formations with ß-substituted dilithiated acrylate systems [6]. Described here is the reaction of 6-cis with ß-ethylthio dilithio acrylate 8a and ß-methoxy dilithio acrylate 8b, which gave diastereospecifically spirotetronate derivatives 9a (81 %) and 9b (40 %), respectively. The structure of compound 9b was assigned by X-ray analysis [12]. Compound 9a was cleanly transformed into 9b via sulfoxide formation with m-chloroperbenzoic acid and methoxide treatment (64 % overall yield).

Saponification of the ester 9a,b with potassium hydroxide led to the corresponding acids 10a, b in 83 % and 85 % yield, respectively. The usefulness of these compounds as intermediates in the synthesis of macrolide antibiotic chlorothricolide 1 [13] was shown by direct lithiation with tert.-butyllithium/lithium cyclohexylisopropyl amide (LCIA) at the α-position of the tetronate moiety of 10b. The required α-hydroxylation was carried out with the methyl borate tert.-butylhydroperoxide/triethylamine system [14]. The α-hydroxylated compound obtained which contains the carbon skeleton, the stereochemistry, and the functional groups of the top half of 1 (R = H) was characterized by treatment with tert.-butyl dimethylsilyl chloride (TBDMS-Cl/imidazole in DMF as disilylated product 11 [15,16].

Scheme 2



	X	R
9a	SEt	Me
9b	OMe	Me
10a	SEt	H
10b	OMe	H

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8) All compounds in Scheme 2 are racemates; only one enantiomer is depicted.

9) Acrylate addition resulted in a 7:3 mixture of both regioisomers. The regioisomer with the carboxylate group in 4-position (7 parts) was desilylated and then obtained as crystalline material.

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12) We are indebted to O. Scheidsteger and G. Huttner for performing an X-ray analysis of compound 9b.
Preparation of 9a,b: To a solution of β-ethylthioacrylic acid or β-methoxyacrylic acid in THF 2 eq tert.-butyllithium were added at -100°C. The reaction mixture was warmed up to -80°C within 2 h. After addition of 1 eq 6-cis the reaction mixture was kept 1 h at -80°C and 4 h at -50°C. The product was obtained by treatment with H_2O/2N HCl, subsequent extraction with CH_2Cl_2, and column chromatography [SiO_2, light petroleum/ethyl acetate (4/1) .]

13) In addition, kijanolide the aglycon of the structurally related macrolide antibiotic kijanimicin should be accessible via the same route. For structural details of kijanimicin see: A.K. Mallams, M.W. Puar, R.R. Rossman, A.T. McPhail, and R.D. Macfarlane, J.Am.Chem.Soc. 103, 3940 (1981).

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15) The isolated products gave satisfactory analytical and spectral data. ^{1}H-NMR (90 MHz, $CDCl_3$, TMS int.): 11: δ 4.62 (d, 1H, -CH(O-R)$_2$; J = 5.2 Hz); 4.12 (s, 3H, OCH_3); 3.9-3.7 (m, 4H, O-CH_2-CH_2-O); 2.7-1.2 (m, 7H, H-6 - H-10); 1.07 (d, 3H, CH_3; J = 7.2 Hz); 0.97 (s, 9H, $SiC(CH_3)_3$); 0.94 (s, 9H, $SiC(CH_3)_3$; 0.3 - 0.25 (4s, 12H, 2 $Si(CH_3)_2$).

16) Treatment of compound 11 in THF, -80°C with LDA and PhSeCl afforded cleanly phenylselenylation α to the tert.-butyldimethylsilyl carboxylate group. This way the ease of forming the required olefin bond at a later stage of the total synthesis of chlorothricolide is disclosed.
^{1}H NMR data of the phenylselenylated compound (250 MHz, $CDCl_3$, TMS int.): δ 7.8-7.2 (m, 5H, SePh); 4.52 (d, 1H, -CH(OR)$_2$; J = 5.1 Hz); 4.8 (s, 3H, OCH_3); 3.6-3.9 (m, 4H, O-CH_2-CH_2-O); 2.5-1.3 (m, 6H, H-6 - H-10); 1.33 (d, 3H, CH_3; J = 6.5 Hz); 0.95 (s, 18H, 2$SiC(CH_3)_3$); 0.2-0.3 (4s, 12H, 2 $Si(CH_3)_2$).

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