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Catalytic Enantioselective Macrolide Synthesis II: Use of Differential Deprotection Protocols[1]

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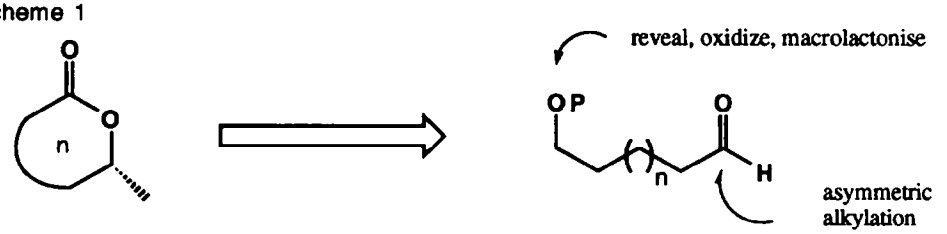
Abstract: Catalytic enantioselective synthesis of Phorcantholide I has been achieved. Key stereochemistry was introduced using a chiral arene chromium tricarbonyl based catalyst to mediate the addition of dimethyl zinc to a functionalised aldehyde. During the synthesis, a method for the selective deprotection of the trityloxy group was revealed and developed.

Ongoing work in this laboratory aimed at application of catalytic asymmetric induction in the synthesis of natural products has recently focused on the macrolide antibiotic agents.[1,2] Antithetic analysis of a variety of such agents (Scheme 1) reveals a versatile strategy *via* a protected hydroxy aldehyde intermediate, the carbonyl group of which can then serve as the building block for introduction of the required asymmetric center. Of particular interest to us was the potential for chiral Lewis acid mediated alkylation control, a protocol which proved successful using the chromium tricarbonyl derived catalyst **1**[3] in the synthesis of *R*-(+)lasiodiplodin.[1] In an effort to develop easy access to a variety of chiral macrolides from readily available precursors, we sought to explore the utility of the hydroxy aldehyde approach, and selected the 10-membered macrolide phorcantholide I[4] to demonstrate the required methodology.

Scheme 1

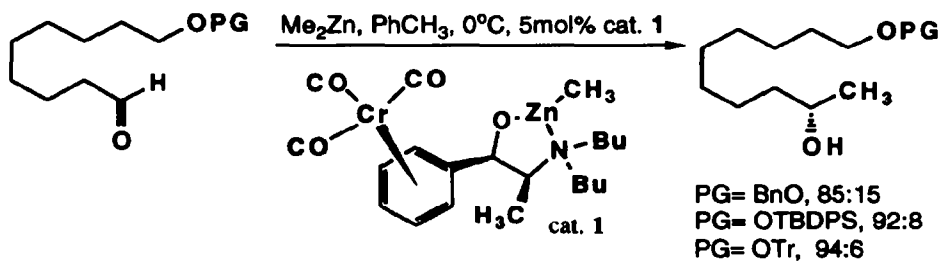


Phorcantholide I has been shown to be a defensive secretion of the longicorn *Pholacantha synonyma*, and has been the focus of a number of synthetic approaches.[4] Our route to *R*-(-)Phorcantholide I began with the monoprotection of 1,9 nonanediol. Oxidation of the remaining alcohol to the corresponding aldehyde then allowed us to probe enantioselective methylation under the influence of our recently developed chromium tricarbonyl derived alkylation catalysts. Such strategy relies on subsequent reprotection of the resulting chiral secondary alcohol in order that the masked primary alcohol be revealed and oxidized to the carboxylic acid. Careful selection of protecting groups for both of these alcohol centers is required; selective deprotection to yield the primary alcohol must be possible, and in addition, UV active chromophores are desirable in order to monitor and optimise enantioexcess from the alkylation reaction using chiral HPLC methods (employing 254 nm UV detection). Initially, a benzyl protected hydroxy aldehyde was used as a substrate for enantioselective alkylation

(Scheme 2), however only moderate (85:15) selectivity was observed. Moving to either a *tert*butyldiphenylsilyloxy (92:8) or trityloxy (94:6) protected system however, selectivity for alkylation was increased to acceptable levels using standard alkylation conditions (typically 5 mol% catalyst **1**).[3]

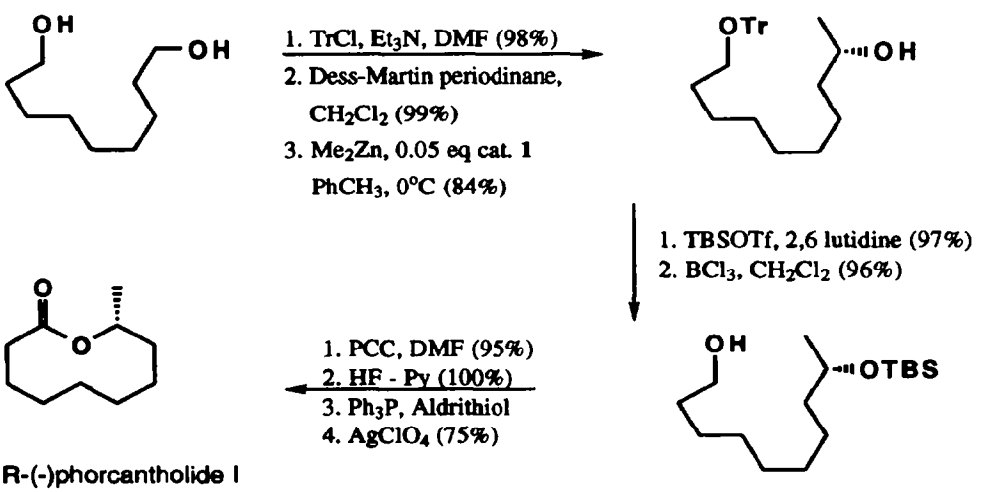
As had been previously observed,[1,3] with related catalysts *devoid of the arene chromium tricarbonyl group* for alkylation control (e.g. N,N dibutylnorephedrine) *far inferior enantioselectivities were observed* (the maximum e.e. obtained for methylation of 9-trityloxy-nonanal was 59% with 20 mol% catalyst).

Scheme 2



With the asymmetric center introduced, and the secondary alcohol protected as a *tert*butyldimethylsilyl ether, the synthesis of phorcantholide I was advanced using the protocol outlined in Scheme 3. Differential deprotection of the trityloxy group in the presence of the silyl ether was critical to the success of the synthesis. Conventional deprotection protocol using either formic acid in ether[5] or diethyl aluminum chloride in methylene chloride[6] failed, giving a mixture of deprotected alcohols. *However, on addition of 1.0 equivalents of boron trichloride, smooth trityloxy deprotection ensued in 30 min at -10°C.*[2] The exposed alcohol was transformed to the

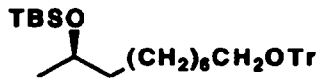
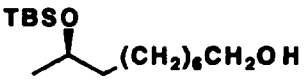
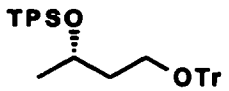
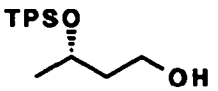
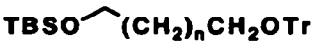
Scheme 3



carboxylic acid, thence the chiral secondary alcohol deprotected to allow macrolactonisation using the pyridyl-thioester protocol.[7] Synthetic phorcantholide I was spectroscopically identical with reported data,[4] and the optical rotation confirmed that racemisation had not taken place during the closing stages of synthesis.[8]

The selective deprotective sequence mandated was investigated further, and proved to have wide applicability (Table 1). Selective boron trichloride mediated detritylation could be achieved in the presence of either primary or secondary *tert*butyldimethylsilyloxy groups, the bulkier *tert*butyldiphenylsilyloxy group and the commonly used benzyloxy group.[9] Isolated yields are typically near to quantitative, and asymmetric centers are preserved intact, making this preferential deprotection strategy advantageous for work involving diol manipulation, where a UV chromophore is desirable in the molecule.

Table 1 Selective Deprotection of Trityl Ethers

Trityl ether	Alcohol	Yield
		96%
		89%
		n= 1-7 91-95%
		95%

Summary: The first *catalytic asymmetric* synthesis of phorcantholide I has been achieved in seven steps from a protected aldehyde. The asymmetric center was introduced using a chiral alkylation catalyst, in ca. 90 % e.e. on a multigram scale. Combination of the asymmetric alkylation methodology and a selective trityloxy deprotective protocol offers a versatile route to a variety of related chiral macrolide agents, the scope of which is currently under study.

Experimental Procedures:

Catalytic asymmetric alkylation of 9-trityloxy-nonanal

To a solution of tricarbonyl chromium (0)(1*R*, 2*S*) N,N-dibutylnorephedrine[3] (0.23g, 0.56 mmol) in toluene (10 mL) at 0 °C was added Me_2Zn (Aldrich, 2M in toluene) dropwise, followed by 9-trityloxy-nonanal (4.5g, 11.3 mmol) in toluene (15 mL). The resulting solution was stirred at 4 °C for 6 days. The solution was poured over ice and extracted with ether (100 mL). The ethereal solution was washed with HCl (1%, 2 x 50 mL), saturated $NaHCO_3$ (1x 50 mL), and water (2 x 50 mL). Column chromatography (90/10 to 70/30 hexanes/ether eluent) yielded (*R*)-(+) 9-trityloxy-2-decanol (3.93 g, 84%) as a colorless oil. $[a]_D$ = +19.0 (c= 0.5, $CHCl_3$);

300 MHz ^{1}H NMR ($CDCl_3$) 7.5-7.2 (m, 15H), 3.83 (br. s, 1H), 3.65 (br. m, 1H), 3.13 (t, 2H, J = 6.5 Hz), 1.8-0.97 (m, 17H); 75MHz ^{13}C NMR ($CDCl_3$) 144.4, 128.6, 127.6, 126.7, 86.2, 67.9, 63.6, 39.2, 30.0, 29.5, 29.5, 29.4, 26.2, 25.7, 23.4; IR (neat) 3388 (br), 3050, 2924, 2848, 1489, 1440, 1363, 1243, 1068 cm^{-1}; MS (m/e) 412 (M^+, 100%); Anal. Calcd for $C_{29}H_{36}O_2$: C, 83.61%; H, 8.71%. Found: C, 83.82%; H 8.69%; HPLC: Diacel OD column; 99:1 hexane:isopropyl alcohol eluent; flow rate 1.0 ml / min; R =18.20 mins, S =18.96 mins.

Selective deprotection of 1-trityloxy-9-t-butyldimethylsilyloxydecane

To a solution of 1-trityloxy-9-t-butyldimethylsilyloxydecane (4.5 g, 8.49mmol) in CH_2Cl_2 (850 mL) at -10 °C was added BCl_3 (1M in CH_2Cl_2, 8.5 mL, 8.5 mmol) dropwise *via* syringe. After 20 minutes at -10 °C, the solution was poured over iced saturated $NaHCO_3$ (100mL), and extracted with CH_2Cl_2 (2 x 50 mL). The organic phase was washed with water (2 x 75 mL) and filtered through a small plug of silica gel. Solvent evaporation afforded 9-*t*-butyldimethylsilyloxy-1-decanol as a colorless oil (2.34 g, 96 %). $[a]_D$ = +1.26 (c= 0.5, $CHCl_3$); 300 MHz ^{1}H NMR ($CDCl_3$) 3.75 (m, 1H), 3.62 (t, 2H, J = 6.6 Hz), 1.6-1.2 (m, 14H), 1.10 (d, 3H, J = 6 Hz), 0.88 (s, 9H), 0.03 (s, 6H); 75 MHz ^{13}C NMR ($CDCl_3$) 68.7, 63.0, 39.7, 32.8, 29.6, 29.6, 29.4, 26.0, 25.8, 25.7, 23.8, 18.2, -4.4; IR (neat) 3339 (br), 2938, 2853, 1461, 1384, 1250, 1138, 1046 cm^{-1}; MS (m/e) 287 (M^+, 1%), 173 (M-TBS, 77), 105 (100); Anal. Calcd for $C_{16}H_{36}O_2Si$: C, 66.60%; H, 12.58%. Found: C, 66.88%; H 12.46%.

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7. For representative example see: Corey, E. J. ; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614.
8. $[\alpha]_D$ = -31.0 (c=0.1, $CHCl_3$); Lit [4b] $[\alpha]_D$ = -32.1 (c=0.56, $CHCl_3$); Lit [10] $[\alpha]_D$ = -35.1 (c=1.0, $CHCl_3$).
9. For a recent report detailing selective deprotection of benzyloxy ethers in the presence of tert butyldiphenyl silyl ethers see Congreve, M. S. ; Davison, E. C. ; Fuhry, M. A. ; Holmes, A. B. ; Payne, A. N. ; Robinson, R. A. ; Ward, S. E. *Synlett.* **1993**, 663.
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