An Efficient High-Yield Synthesis of D-*ribo*-Phytosphingosine[†]

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ABSTRACT



 $[4R-[4\alpha(S^*),5\alpha]]$ -2,2-Dimethyl-4-(2-oxo-5-vinyl[1,3]dioxolan-4-yl)oxazolidine-3-carboxylic acid *tert*-butyl ester 5a, obtained in excellent yield and diastereoselectivity by the α -hydroxyallylation of the Garner aldehyde (4), is exploited in a novel high-yield synthesis of D-*ribo*-phytosphingosine (8), using microwave-enhanced cross metathesis as the key step in the chain elongation.

As a part of our ongoing research on the stereocontrolled synthesis of alk-1-en-3,4-diols,¹ we recently proposed 3-bromopropenylmethylcarbonate 1 as a novel precursor of monoprotected diols 2 (Scheme 1)².



The reaction of **1** with zinc metal in water affords a γ -ethero-substituted allylic organometallic compound, which promptly adds to a carbonyl compound to give **2** in very high isolated yields. When the same reaction is carried out with indium metal in *N*,*N*-dimethylformamide (DMF) as the solvent, the cyclic oxazolidin-2-ones **3** are directly obtained

in almost quantitative yields, either adopting a one-step Barbier protocol or a two-step Grignard procedure (Scheme 2).³



Having in our hands quite a simple and efficient reaction protocol for the α -hydroxyallylation of carbonyl compounds, we envisioned in (*S*)-*N*-Boc-serinal acetonide **4**⁴ (Garner aldehyde)⁵ an interesting substrate to approach the 2-amino-1,3,4-triol motif present in a variety of natural products, i.e., phytosphingosines. To our delight, the foregoing reaction protocol afforded cyclic carbonate **5a** in 87% isolated yield (Scheme 3).

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 $^{^{\}dagger}$ Dedicated to Prof. Achille Umani-Ronchi on the occasion of his 70th birthday.

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Following a typical Grignard procedure, 3-bromopropenylmethylcarbonate **1** was added at 0 °C to a suspension of indium powder in anhydrous DMF and the heterogeneous mixture was stirred for 1 h at 0 °C. Garner aldehyde **4** was then added, and the reaction mixture was stirred for 3 h at 0 °C and for an additional hour at room temperature, to allow complete cyclization of the intermediate indium alkoxides. GC-MS analysis of the crude reaction mixture revealed the presence of three peaks in a 91:7:2 relative ratio, corresponding to **5a** and two minor isomeric products on the basis of mass analysis. The mixture of the three isomers was isolated in 98% overall yield after purification by SiO₂ flash chromatography (Table 1, entry 1). The major stereoisomer

Table 1. α -Hydroxyallylation of the Garner Aldehyde								
entry	metal	solvent	temp (°C) ^{a}	yield $(\%)^b$	$5a:5b:5c^{c}$			
1	In	DMF	0	98	91:7:2			
2	In	DMF	-20	95	91:7:2			
3	In	DMF	-60	98	91:7:2			
4	In	THF	-78	75	91:7:2			
5	Zn	DMF	-60	97	91:7:2			
6	Zn	THF	-78	68	91:7:2			

^{*a*} Temperature of the addition step. ^{*b*} Isolated yields after purification by flash chromatography. ^{*c*} Diastereomeric ratio determined on the crude reaction mixture by gas chromatography.

5a was quantitatively isolated as a white solid by crystallization from diethyl ether/pentane (1:1) at -20 °C; the absolute configuration of **5a** was unambiguously established by comparison of its optical and spectroscopical data with the known enantiomer of the title compound,⁶ while no attempt was made to assign the absolute stereochemistry of the two minor isomers **5b** and **5c**. To improve the diastereoselectivity of the addition reaction the possible effect of temperature, solvent, and metal was investigated (Table 1), but to our surprise, the relative 91:7:2 diastereomeric ratio never changed. Other examples of nucleophilic additions where stereoselectivity is invariant with respect to temperature were recently reported in the literature.⁷ In these cases it was claimed that the selectivity was controlled by entropic rather than by enthalpic factors.

The absolute stereochemistry of the major isomer 5a is the result of an excellent control of both facial and simple diastereoselectivity, in analogy to the observed outcome of the α -hydroxyallylation of 4 with 3-bromopropenyl acetate and indium, in a synthesis of 1,4-dideoxy-1,4-L-iminoribitol.^{4a} With regard to simple diastereoselectivity, we have previously reported that **1** in the presence of either indium or zinc adds to aliphatic aldehydes with high levels of anti diastereopreference, independently of the E/Z composition of starting bromide 1.^{2,3} A theoretical study (DFT B3LYP, basis set: 3-21G* and 6-311G) on the simple selectivity displayed by zinc complexes deriving from (E)- and (Z)-3-bromopropenyl acetate with aliphatic aldehydes is underway, and preliminary results confirm the stereoconvergence of the two stereoisomeric (E)- and (Z)-allylzinc complexes to the anti adduct, due to diastereomorphic chairlike transition states.⁸

Since the heterosubstituent stereopattern present in **5a** perfectly matches the polar terminus structure of D-*ribo*-phytosphingosine (**8**),^{9,10} a straightforward route to **8** was envisaged, based on a cross-metathesis (CM) reaction¹¹ with 1-tetradecene (**6**) to achieve the required chain elongation process (Scheme 4).



Preliminary screening experiments in refluxing dichloroethane (DCE) with 2 equiv of **6** and Grubbs first generation catalyst **A** (Figure 1) did not furnish any cross-coupled product, while Grubbs second generation catalyst **B** (Figure 1) afforded the desired product in 65% isolated yield after 24 h.

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To increase the CM step efficiency and to shorten the reaction time, we decided to test microwave (MW) heating, as recently reported by Poulsen using *N*-allyl amino acid substrates.¹² Results obtained in DCE as the solvent are reported in Table 2.

Table 2.	MW-Enhanced Synthesis of 7 by Cross-Metathesis ^a					
entry	B (%)	6 (equiv)	time (min)	7, yield $(\%)^b$		
1	10	2	5	79		
2	5	2	5	76		
3	3.5	2	5	77		
4	3	2	5	70		
5	1	2	15	23		
6	3.5	3	15	93		

^{*a*} Power = 200 W, $T \sim 90$ °C; for temperature–time profile see the Supporting Information. ^{*b*} Isolated yields after purification by flash chromatography.

Adopting the same reaction conditions for thermal CM, but using MW heating, we were able to obtain **7** in 79% isolated yield after only 5 min of irradiation at 200 W (Table 2, entry 1). Grubbs catalyst **B** can be reduced from 10% down to 3.5% without appreciable reduction in overall isolated yields (Table 2, entries 1–3), while with lower amounts the yields dropped considerably (Table 2, entries 4 and 5). Finally, by using 3 equiv of **6** we were able to isolate **7** in 93% yield after 15 min (Table 2, entry 6). The CM reaction favored the formation of (*E*)-**7** in more than 80:20 *E*/*Z* ratio; however, stereochemical outcome did not matter, since completion of the D-*ribo*-phytosphingosine **8** synthesis required hydrogenation of the double bond and removal of the protective groups.

Unfortunately, the simple hydrogenation of the double bond with Pd/C in MeOH afforded a plethora of byproducts, presumably due to the insertion of palladium metal into the cyclic allylic carbonate moiety of **7**. So we decided to remove the carbonate protective group using basic conditions before hydrogenation, without isolation of any intermediate (Scheme 5).



During the hydrogenation step in MeOH, a partial hydrolysis of the oxazolidine ring to give **11** occurred spontaneously. However, the final product **8** was easily obtained by a simple acid hydrolysis with trifluoroacetic acid/water (20:1) of the crude reaction mixture of **10** and **11**. After vacuum evaporation of excess TFA, neutralization with aq NaHCO₃, and extraction with AcOEt, **8** was isolated in 92% overall yield starting from **7** by flash chromatography on silica gel, using NH₃/CH₃OH/CHCl₃ (1.5/15/85). Optical and spectroscopic data were in excellent agreement with those reported in the literature.¹³

In summary, we have reported a very efficient 5-step synthesis of D-*ribo*-phytosphingosine starting from Garner aldehyde in 75% overall isolated yield.

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Supporting Information Available: Detailed experimental procedures and copies of ¹H and ¹³C NMR spectra of compounds **5a**, **7**, and **8**. This material is available free of charge via the Internet at http://pubs.acs.org.

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