ORGANIC LETTERS

2006
Vol. 8, No. 15
3303−3305

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

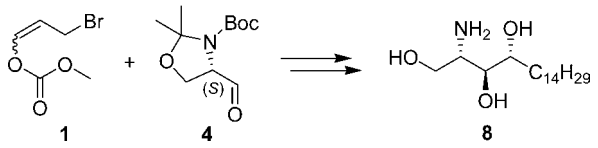
Marco Lombardo,* Montse Guiteras Capdevila, Filippo Pasi, and Claudio Trombini*

Dipartimento di Chimica "G. Ciamician", Università di Bologna, via Selmi 2, 40126, Bologna, Italy

marco.lombardo@unibo.it; claudio.trombini@unibo.it

Received May 17, 2006

ABSTRACT

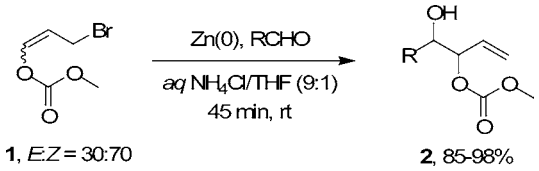


1 4 8

[4*R*-[4α(*S),5α]]-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].

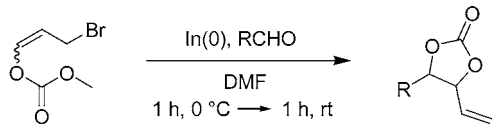
Scheme 1. Synthesis of Monoprotected Diols **2**



1, *E*:*Z* = 30:70 **2**, 85-98%

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]

Scheme 2. One-Pot Synthesis of Cyclic Carbonates **3**



1, *E*:*Z* = 30:70 **3**, 88-98%

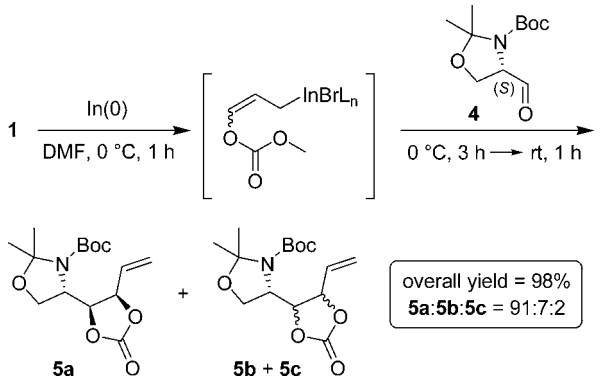
Having in our hands quite a simple and efficient reaction protocol for the α-hydroxyallylation of carbonyl compounds, we envisioned in (*S*)-*N*-Boc-serinal acetonide **4**[4] (Garner aldehyde)[5] an interesting substrate to approach the 2-amino-1,3,4-triol motif present in a variety of natural products,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

† Dedicated to Prof. Achille Umani-Ronchi on the occasion of his 70th birthday.

(1) Lombardo, M.; Licciulli, S.; Trombini, C. *Pure Appl. Chem.* **2004**, *76*, 657.
(2) Lombardo, M.; Pasi, F.; Tiberi, C.; Trombini, C. *Synthesis* **2005**, 2609.
(3) Lombardo, M.; Pasi, F.; Trombini, C. *Eur. J. Org. Chem.* In press.
(4) (a) Lombardo, M.; Licciulli, S.; Trombini, C. *Tetrahedron Lett.* **2003**, *44*, 9147. (b) Lombardo, M.; Gianotti, K.; Licciulli, S.; Trombini, C. *Tetrahedron* **2004**, *60*, 11725.
(5) Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2136.

10.1021/ol0612096 CCC: $33.50
Published on Web 06/21/2006

Scheme 3. α-Hydroxyallylation of Garner Aldehyde



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 SiO_2 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

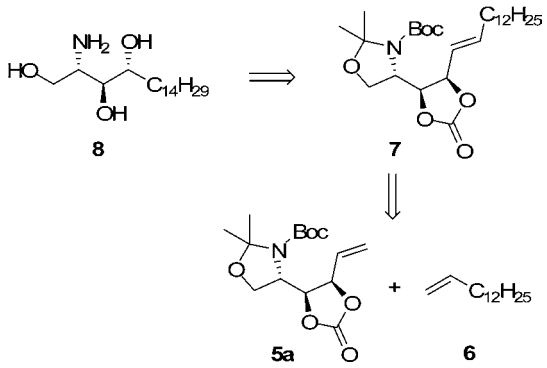
[a] Temperature of the addition step. [b] Isolated yields after purification by flash chromatography. [c] Diastereomeric ratio determined on the crude reaction mixture by gas chromatography.

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) reaction[11] with 1-tetradecene (**6**) to achieve the required chain elongation process (Scheme 4).

Scheme 4. Retrosynthetic Strategy for the Synthesis of **8**



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.

(6) **5a**: mp 82−84 °C; $[\alpha]^{D}_{20}$ −73 (*c* 1.2, $CHCl_3$). Barret, A. G. M.; Malecha, J. W. *J. Chem. Soc., Prekin Trans. 1* **1994**, 1901: mp 82−83 °C; $[\alpha]^{D}_{20}$ +73 (*c* 1.2, $CHCl_3$).

(7) (a) Berardi, R.; Cainelli, G.; Galletti, P.; Giacomini, D.; Gualandi, A.; Muccioli, L.; Zannoni, C. *J. Am. Chem. Soc.* **2005**, *127*, 10669 and references therein. (b) Lombardo, M.; Fabbroni, S.; Trombini, C. *J. Org. Chem.* **2001**, *66*, 1264.

(8) Bottoni, A. et al. Manuscript in preparation.

(9) Howell, A. R.; Ndakala, A. J. *Curr. Org. Chem.* **2002**, *6*, 365.

(10) Phytosphingosines are major membrane components in plants and yeasts, and have been found to act in mammals as enzyme inhibitors and as citotoxic agents against leukemic cell lines: (a) Schneiter, R. *Bioessays* **1999**, *21*, 1004. (b) Sharma C.; Smith, T.; Li, S.; Schroepfer, G. J., Jr.; Needleman, D. H. *Chem. Phys. Lipids* **2000**, *104*, 1. (c) Tamiya-Koizumi, K.; Murate, T.; Suzuki, M.; Simbulan, C. M. G.; Nakagawa, M.; Takemura, M.; Furuta, K.; Izuta, S.; Yoshida, S. *Biochem. Mol. Biol. Int.* **1997**, *41*, 1179.

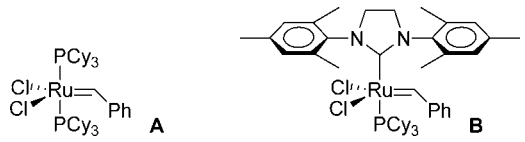


Figure 1. Grubbs first (**A**) and second generation (**B**) catalysts.

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]

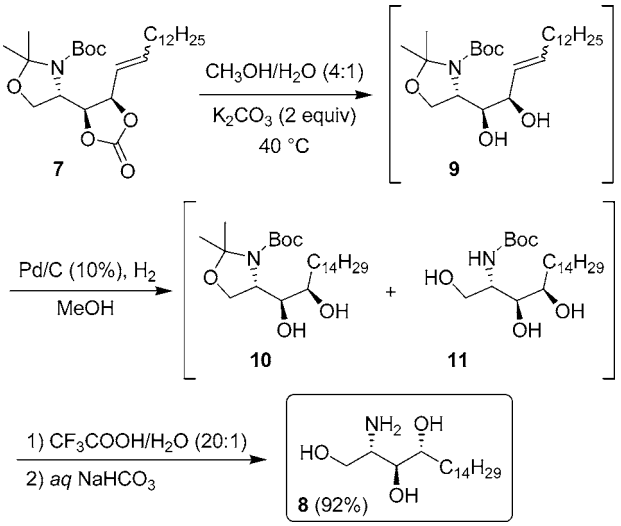
entry	**B** (%)	**6** (equiv)	time (min)	**7**, yield (%)[b]
1	10	2	5	79
2	5	2	5	76
3	3.5	2	5	77
4	3	2	5	70
5	1	2	15	23
6	3.5	3	15	93

[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).

Scheme 5. Synthesis of d-*ribo*-Phytosphingosine



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 $NaHCO_3$, and extraction with AcOEt, **8** was isolated in 92% overall yield starting from **7** by flash chromatography on silica gel, using $NH_3/CH_3OH/CHCl_3$ (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.

Acknowledgment. This work was supported by a MIUR (Rome) PRIN project grant: "Sintesi e Stereocontrollo di Molecole Organiche per lo Sviluppo di Metodologie Innovative di Interesse Applicativo".

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

OL0612096

(11) For recent examples of carbon chain elongation strategies via CM see: (a) D-*erythro*- and D-*threo*-sphingosine: Chaudhari, V. D.; Ajish Kumar, K. S.; Dhavale, D. D. *Org. Lett.* **2005**, 5805. (b) D-*erythro*-Sphingosine: Torrsell, S.; Somfai, P. *Org. Biomol. Chem.* **2004**, *2*, 164. (c) L-*xylo*- and L-*arabino*-phytosphingosines: Singh, O. V.; Kampf, D. J.; Han, H. *Tetrahedron Lett.* **2004**, *45*, 7239. (d) D-*erythro*-Ceramide: Rai, A. N.; Basu, A. *Org. Lett.* **2004**, *6*, 2861. (e) α-C-galactosylceramide immunostimulants: Chen, G.; Schmieg, J.; Tsuji, M.; Franck, R. W. *Org. Lett.* **2004**, *6*, 4077.

(12) Poulsen, S.-A.; Bornaghi, L. F. *Tetrahedron Lett.* **2005**, *46*, 7389.

(13) **8**: mp 100−102 °C, $[\alpha]^D_{20}$ +10.3 (*c* 1.0, C_5H_5N). (a) He, L.; Byun, H.-S.; Bittman R. *J. Org. Chem.* **2000**, *65*, 7618: $[\alpha]^D_{20}$ +9.7 (*c* 0.7, C_5H_5N). (b) Murakami, T.; Taguchi, K *Tetrahedron* **1999**, *55*, 989: mp 98−101 °C, $[\alpha]^D_{20}$ +8.7 (*c* 0.8, C_5H_5N). (c) Imashiro, R.; Sakurai, O.; Yamashita, T.; Horikawa, H. *Tetrahedron* **1998**, *54*, 10657: $[\alpha]^D_{20}$ +9.5 (*c* 1.0, C_5H_5N). (d) Li, Y.-L.; Mao, X.-H.; Wu, Y.-L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1559: $[\alpha]^D_{20}$ +8.9 (*c* 0.6, C_5H_5N). (e) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439: mp 98−100 °C. (f) Mulzer, J.; Brand, C. *Tetrahedron* **1986**, *42*, 5961: mp 103 °C; $[\alpha]^D_{20}$ +7.9 (*c* 1.2, C_5H_5N).