Enantioselective Synthesis of the C1–C15 Fragment of Dolabelide C

Aurélie Vincent, Joëlle Prunet*

Laboratoire de Synthèse Organique, UMR CNRS 7652, Ecole Polytechnique, DCSO, 91128 Palaiseau, France
Fax +33(1)69333851; E-mail: joelle.prunet@polytechnique.fr

Received 18 May 2006

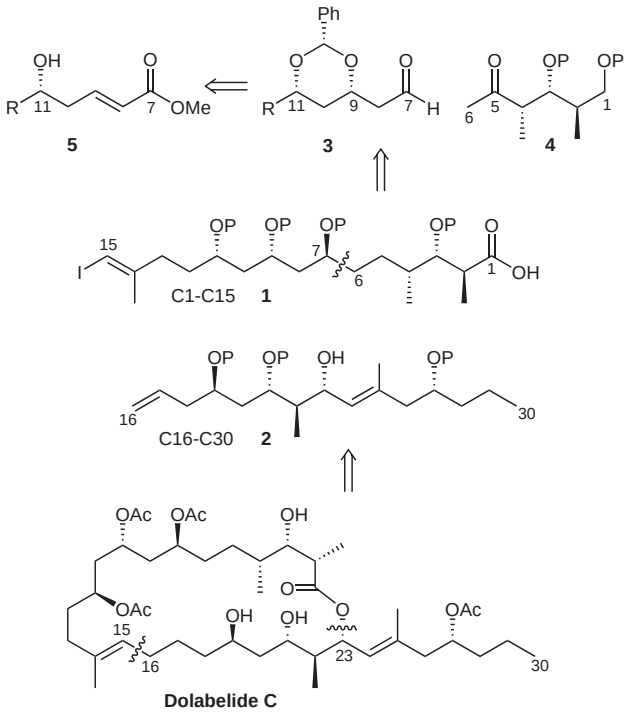
Abstract: A synthesis of the C1–C15 fragment of dolabelide C is reported. The key step is a diastereoselective Mukaiyama aldol reaction to form the C6–C7 bond, followed by reduction and deoxygenation of the carbonyl group at C5. The trisubstituted vinyl iodide is introduced via the corresponding vinyl boronate by cross metathesis.

Key words: stereoselective synthesis, aldol reactions, metathesis, Michael additions, acetals

In 1995, Yamada and co-workers isolated dolabelides A and B, two 22-membered ring lactones, from the sea hare *Dolabella auricularia* (family Aplysiidae).[1] In 1997, two similar 24-membered ring lactones, dolabelides C and D, were also extracted from the same source.[2] These compounds were shown to exhibit cytotoxicity against HeLa-S_3 cell lines with IC_{50} values of 6.3, 1.3, 1.9, and 1.5 μg/mL, respectively. Their structures were determined by FAB high resolution mass spectroscopy and 2D NMR; their absolute configuration was determined by the modified Mosher method.[3] Several groups have reported syntheses of dolabelide fragments,[4] and the total synthesis of dolabelide D was very recently completed by Leighton and co-workers.[5]

We chose dolabelide C as a potential target, but the strategy we designed could be applied to the other members of the family. The retrosynthesis we envisaged is illustrated in Scheme 1. Opening of the macrolactone, followed by disconnection through the C15–C16 bond furnishes compounds **1** and **2** of roughly equal complexity. These two fragments would be joined by a Suzuki coupling between the vinyl iodide at C15 and a borane derived from the alkene at C16. A macrolactonization would then close the ring.

We report here the synthesis of the C1–C15 fragment of dolabelide C. Compound **1** could be assembled by a diastereoselective aldol reaction between aldehyde **3** and ketone **4** (Scheme 1), and the extra carbonyl group at C5 would be reduced in later steps. The protected *syn*-1,3-diol functional group at C9 and C11 would be installed by an intramolecular conjugate addition of a hemiacetal anion made in situ from homoallylic alcohol **5** and benzaldehyde under basic conditions.[6]

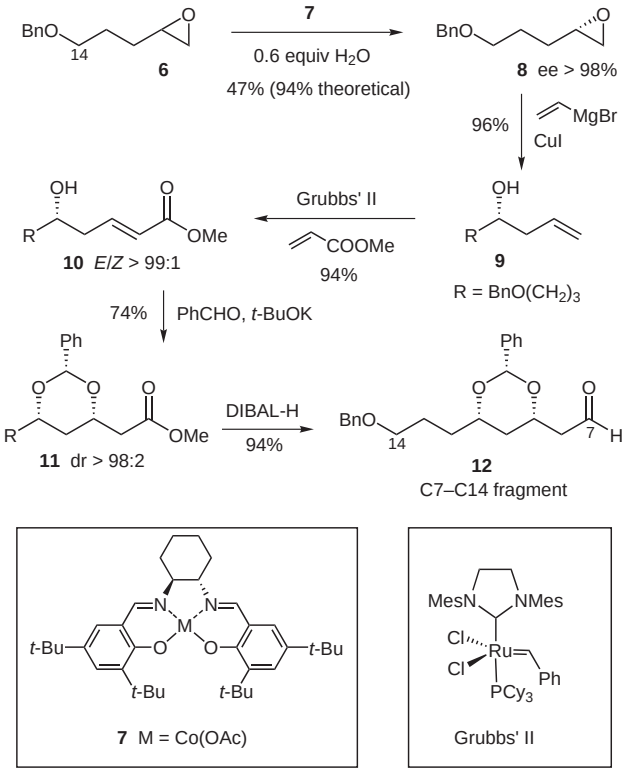


Scheme 1

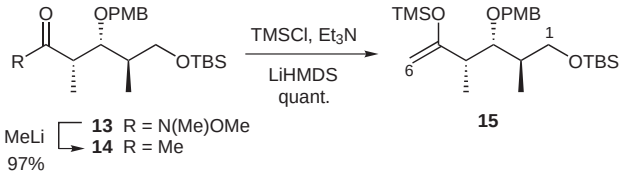
The known epoxide **6**[7] with a benzyloxy group at C14 was chosen as a precursor for the C7–C14 portion of the target molecule (Scheme 2). The C15 carbon would be added at a late stage of the synthesis. Jacobsen's HKR[8] of this epoxide, catalyzed by salen complex **7**, furnished the corresponding homochiral epoxide **8** in 47% yield (94% theoretical) with an excellent ee. Opening of the epoxide moiety with vinylmagnesium bromide in the presence of a catalytic amount of CuI gave homoallylic alcohol **9** in 96% yield. Cross metathesis of this compound with methyl acrylate and second generation Grubbs' catalyst[9] in dichloromethane at reflux led to unsaturated ester **10** as the *E* isomer exclusively in excellent yield. Benzylidene acetal **11** was obtained by treatment of homoallylic alcohol **10** with benzaldehyde and *t*-BuOK, and the ester function was reduced with DIBAL-H at –95 °C to give aldehyde **12** in excellent yield.

The C1–C6 ketone **14** (Scheme 3) was prepared by the addition of MeLi to the corresponding Weinreb amide **13**, which was reported by Heathcock and co-workers during their study towards the synthesis of discodermolide.[10] The corresponding trimethylsilyl enol ether **15** was formed in quantitative yield.

SYNLETT 2006, No. 14, pp 2269–2271
Advanced online publication: 24.08.2006
DOI: 10.1055/s-2006-949614; Art ID: D14406ST



Scheme 2

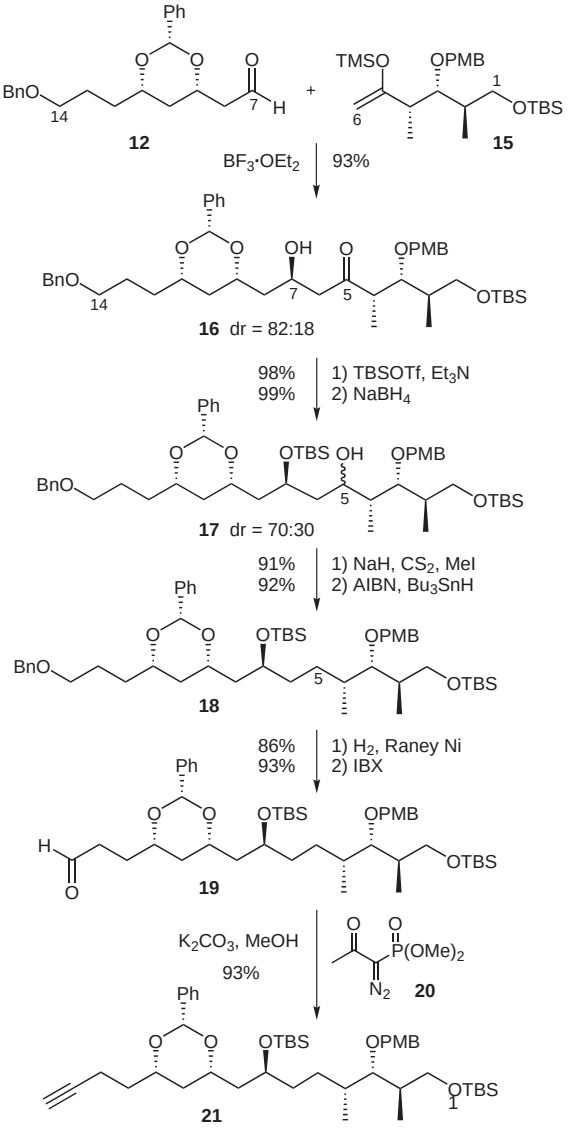


Scheme 3

The Mukaiyama aldol reaction between silyl enol ether **15** and aldehyde **12** is controlled by the aldehyde, furnishing the 1,3-*anti* product **16** as the major diastereomer (82:18 ratio) in 93% yield (Scheme 4).[11] The major diastereomer was isolated in 75% yield after further chromatography. After protection of alcohol **16** as its TBS ether, the next operation involved complete reduction of the C5 ketone, which is not present in the natural product. This carbonyl group was first reduced with $NaBH_4$, and the resulting alcohols **17** were converted into the corresponding xanthates. Deoxygenation proceeded smoothly with Bu_3SnH and AIBN in toluene at reflux[12] to give compound **18** in 81% overall yield (four steps) from **16**.

To complete the synthesis of the C1–C15 portion of dolabelide C, a vinyl iodide moiety had to be appended to C14. For this purpose, the primary benzyloxy group was selectively hydrogenolyzed in the presence of the PMB ether and the benzylidene acetal with Raney nickel.[13] The resulting alcohol was oxidized with iodoxybenzoic acid (IBX)[14] to furnish aldehyde **19**. This aldehyde was then converted into the terminal alkyne **21** with Ohira's reagent **20**[15] in good yield. We had planned to use Negishi's Zr-catalyzed carboalumination to introduce the methyl group and the terminal iodide.[16] Unfortunately, all our attempts to obtain compound **23** were unsuccessful. No reaction occurred at low temperature even in the presence of a small amount of water,[17] and decomposition was observed at higher temperatures.

We also tried to prepare a vinyl silane derivative which could be easily converted to **23**, but silylcupration followed by quenching with MeI[18] was not regioselective for compound **21**, and the methyl group was not incorporated. Use of $MeMgSnBu_3$/MeI did not lead either to the corresponding vinyl stannane.[19]

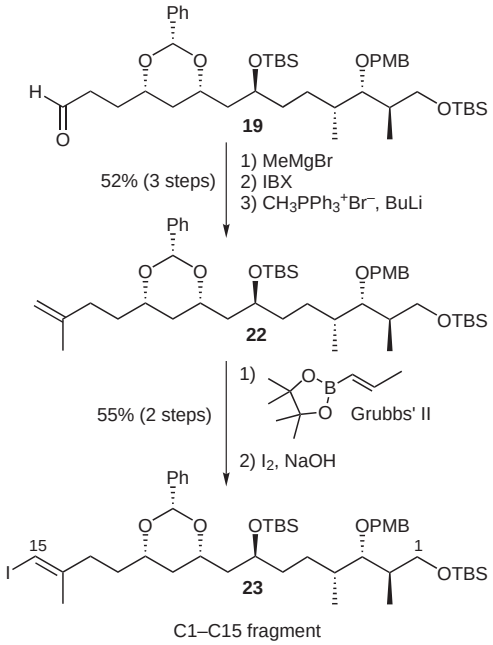


Scheme 4

Aldehyde **19** was then homologated to the corresponding ketone in 2 steps (Scheme 5), but conversion of this intermediate into the vinyl iodide using the Takai method[20] was not possible. Finally, this ketone was transformed into the *gem*-disubstituted olefin **22** (65% yield along with 26% recovered ketone),[21] and cross metathesis

with the required boronate followed by boron–iodine exchange furnished **23** as a 2:1 mixture of *E*/*Z* isomers.[22] The pure *E* olefin[23] could be isolated in 55% yield by preparative HPLC.

In conclusion, we have synthesized the C1–C15 fragment of dolabelide C in a convergent manner in 17 steps for the longest linear sequence (11.4% overall yield from **6**). The key step is a diastereoselective Mukaiyama aldol to form the C6–C7 bond and establish the C7 stereocenter.



Scheme 5

Acknowledgment

Financial support was provided by the CNRS and the Ecole Polytechnique. A.V. acknowledges the Délégation Générale pour l'Armement (DGA) for a fellowship. We thank Jean-Pierre Pulicani for HPLC purification of compound **23**.

References and Notes

(1) Ojika, M.; Nagoya, T.; Yamada, K. *Tetrahedron Lett.* **1995**, *36*, 7491.
(2) Suenaga, K.; Nagoya, T.; Shibata, T.; Kigoshi, H.; Yamada, K. *J. Nat. Prod.* **1997**, *60*, 155.
(3) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
(4) (a) C16–C24: Grimaud, L.; de Mesmay, R.; Prunet, J. *Org. Lett.* **2002**, *4*, 419. (b) C15–C24 and C25–C30: Desroy, N.; Le Roux, R.; Phansavath, P.; Chiummiento, L.; Bonini, C.; Genêt, J.-P. *Tetrahedron Lett.* **2003**, *44*, 1763. (c) C1–C13: Le Roux, R.; Desroy, N.; Phansavath, P.; Genêt, J.-P. *Synlett* **2005**, 429. (d) C15–C30: Schmidt, D. R.; Park, P. K.; Leighton, J. L. *Org. Lett.* **2003**, *5*, 3535. (e) C1–C13: Keck, G. E.; McLaws, M. D. *Tetrahedron Lett.* **2005**, *46*, 4911.
(5) Park, P. K.; O'Malley, S. J.; Schmidt, D. R.; Leighton, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 2796.
(6) Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446.
(7) Lowik, D. W. P. M.; Liskamp, R. M. J. *Eur. J. Org. Chem.* **2000**, 1219.
(8) (a) Chow, S.; Kitching, W. *Tetrahedron: Asymmetry* **2002**, *13*, 779. (b) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421.
(9) (a) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953. (b) Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 3172.
(10) The key step of the synthesis of amide **13** is an Evans aldol reaction with an aldehyde derived from the Roche ester: Clark, D. L.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 5878.
(11) Evans, D. A.; Coleman, P. J.; Côté, B. *J. Org. Chem.* **1997**, *62*, 788.
(12) (a) Ozawa, T.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **2001**, *66*, 3338. (b) Barton, D. H. R.; Dorchak, J.; Jaszberenyi, J. Cs. *Tetrahedron* **1992**, *48*, 7435.
(13) Vincent, A.; Prunet, J. *Tetrahedron Lett.* **2006**, *47*, 4075.
(14) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, *64*, 4537.
(15) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521. (c) Davies, H. M. L.; Cantrell, W. R.; Romines, K. R.; Baum, J. S. *Org. Synth.* **1992**, *70*, 93.
(16) Negishi, E.-i.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639.
(17) Wipf, P.; Lim, S. *Angew. Chem. Int. Ed.* **1993**, *32*, 1068.
(18) (a) Barbero, A.; Cuadrado, P.; Fleming, I.; Gonzalez, A. M.; Pulido, F. J.; Sanchez, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1525. (b) Fleming, I.; Newton, T.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527.
(19) Uenishi, J.; Kawahama, R.; Yonemitsu, O. *J. Org. Chem.* **1997**, *62*, 1691; this reaction was performed on a model compound.
(20) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
(21) This reaction has not been optimized.
(22) Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031.
(23) Spectroscopic data for compound **23**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51 (dd, *J* = 7.9, 1.5 Hz, 2 H, Ph), 7.35–7.40 (m, 3 H, Ph), 7.27 (d, *J* = 8.6 Hz, 2 H, PMB), 6.86 (d, *J* = 8.6 Hz, 2 H, PMB), 5.94 (dd, *J* = 2.1, 1.3 Hz, 1 H, CH-15), 5.48 (s, 1 H, C*H*Ph), 4.53 (d, *J* = 10.8 Hz, 1 H, C*H*HPh), 4.49 (d, *J* = 11.0 Hz, 1 H, CH*H*Ph), 3.98–4.18 (m, 2 H, CH-7, CH-9), 3.78–3.82 (m, 1 H, CH-11), 3.79 (s, 3 H, OCH_3), 3.72 (dd, *J* = 9.6, 5.2 Hz, 1 H, CH-1), 3.63 (dd, *J* = 9.6, 3.0 Hz, 1 H, CH-1), 3.27 (dd, *J* = 8.7, 2.2 Hz, 1 H, CH-3), 2.35–2.48 (m, 2 H, CH_2-13), 1.87 (d, *J* = 1.2 Hz, 3 H, CH_3-14), 1.78–1.84 (m, 2 H, CH-2, CH-12), 1.30–1.75 (m, 10 H, CH-4, CH_2-5, CH_2-6, CH_2-8, CH_2-10, CH-12), 0.89–0.97 [m, 24 H, $SiC(CH_3)_3$, CH_3-2, CH_3-4], 0.09, 0.08, 0.06 [s, 12 H, $Si(CH_3)_2$]. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.6 (C-14), 158.9, 138.9, 131.6, 129.1, 128.5, 128.1, 126.0, 113.7 (Ar), 100.2 (*C*HPh), 83.6 (C-3), 75.9 (C-11), 74.9 (C-15), 74.5 (CH_2Ph), 73.0 (C-9), 67.9 (C-7), 65.0 (C-1), 55.3 (OCH_3), 43.3 (C-6), 38.6 (C-2), 37.5 (C-10), 36.3 (C-8), 35.6 (C-4), 35.1 (C-13), 33.9 (C-12), 29.6 (C-5), 26.0 [$SiC(CH_3)_3$], 24.0 (CH_3-14), 18.3, 18.1 (SiC), 14.7 (CH_3-2), 13.5 (CH_3-4), –4.1, –4.5, –5.3, –5.4 [$Si(CH_3)_2$]. HRMS (EI): *m*/*z* calcd for $C_{45}H_{75}O_6I_1Si_2$: 894.4147; found: 894.4155.