ORGANIC LETTERS

2002
Vol. 4, No. 3
419−421

Diastereoselective Synthesis of Protected *syn* 1,3-Diols: Preparation of the C16–C24 Portion of Dolabelides

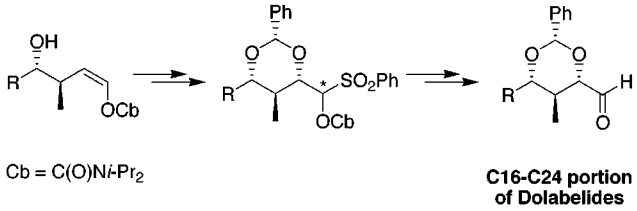
Laurence Grimaud,[†] Romain de Mesmay,[†] and Joëlle Prunet*[,‡]

Laboratoire Chimie et Procédés, Ecole Nationale Supérieure des Techniques Avancées, 32 boulevard Victor, F-75015 Paris, France, and Laboratoire de Synthèse Organique, UMR CNRS 7652, Ecole Polytechnique, DCSO, F-91128 Palaiseau, France

joelle.prunet@polytechnique.fr

Received November 26, 2001

ABSTRACT



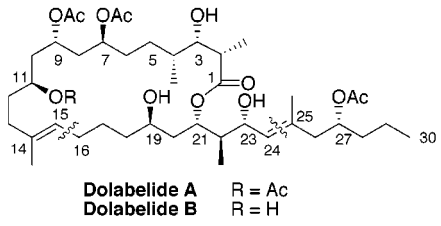
Cb = C(O)N*i*-Pr$_2$

C16-C24 portion of Dolabelides

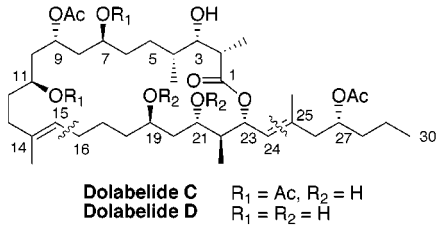
We have designed a new method to make synthons encompassing a protected *syn* 1,3-diol motif and an aldehyde α to the 1,3-dioxane ring. An additional stereocenter was also created, potentially leading to stereochemically defined 1,2,4-triols. This method was successfully applied to the synthesis of the C16–C24 portion of Dolabelides.

In 1995, Dolabelides A and B were isolated from Japanese specimens of the sea hare *Dolabella auricularia* (family Apysiidae).[1] Two parent compounds, Dolabelides C and D, were extracted from the same source in 1997 (Figure 1).[2] These macrolides exhibit cytotoxicity against HeLaSe$_3$ cell lines with IC$_{50}$ values of 6.3, 1.3, 1.9, and 1.5 μg/mL, respectively. Their structures were determined by spectroscopic techniques such as HRFABMS and 2D NMR, and their absolute configuration was ascertained by applying the modified Mosher method.[3]

The retrosynthesis we envisioned is shown in Scheme 1. Dolabelides can be disconnected in two roughly equal fragments C1−C15 and C16−C30. The macrocycle would be constructed by a Suzuki coupling[4] between a vinyl iodide at C15 and a borane derived from the olefin at C16, followed by a macrolactonization involving the appropriate hydroxyl function (C21 for the A, B series and C23 for the C, D



Dolabelide A R = Ac
Dolabelide B R = H



Dolabelide C R_1 = Ac, R_2 = H
Dolabelide D R_1 = R_2 = H

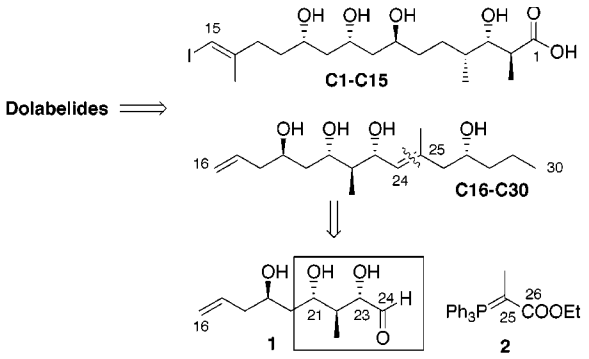
Figure 1. Structures of Dolabelides A, B, C, and D.

[†] Ecole Nationale Supérieure des Techniques Avancées.
[‡] Ecole Polytechnique.

(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) For a recent use of such a coupling reaction, see: Sawada, D.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 209 and references therein.

10.1021/ol017122w CCC: $22.00
Published on Web 01/12/2002

Scheme 1

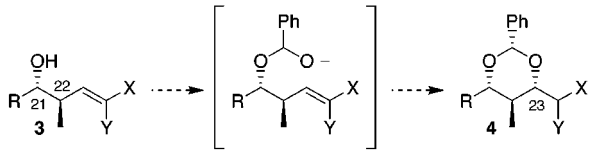


series). The order of events could also be reversed. The C16−C30 portion would be made from aldehyde **1**, using a Wittig reaction to install the trisubstituted double bond between C24 and C25.

We report here the synthesis of the C16−C24 synthon **1** of Dolabelides, which involves a new method for the construction of the C21−C23 stereotriad.

We planned to introduce the hydroxyl group at C23 by an intramolecular conjugate addition of a hemiacetal anion made *in situ* from homoallylic alcohol **3** and benzaldehyde in the presence of a catalytic amount of potassium *tert*-butoxide, which would lead to compound **4** (Scheme 2).

Scheme 2



A conjugate addition of this type has been reported by Evans and Prunet,[5] where X is an ester or a Weinreb amide (and Y is a proton). In our case, X and Y should be easily converted into an aldehyde moiety, and one of them should be a Michael acceptor. To that aim, a sulfone was selected to be the electron-withdrawing group X; Y could then be a protected alcohol. We chose the carbamate group designed by Hoppe, because precursors of **3** (such as **5**, see Scheme 3) could be prepared diastereoselectively and enantioselectively by a homoaldol reaction,[6] which installs both stereocenters at C21 and C22.

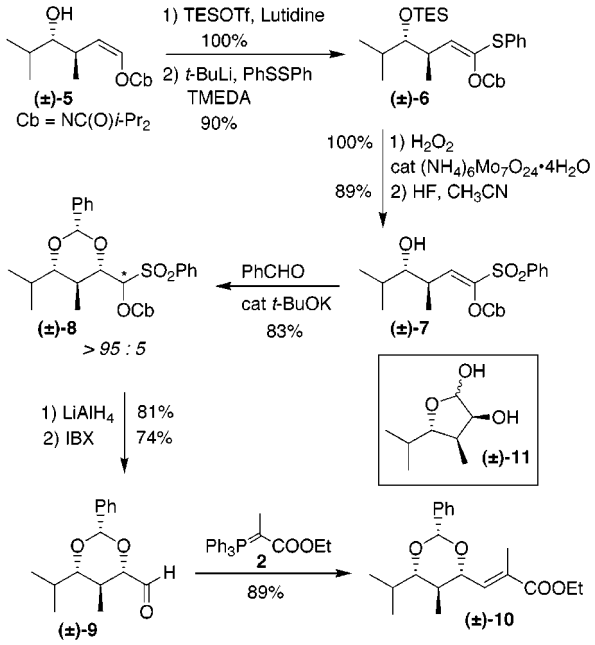
The feasibility of the methodology was tested on model compound (±)-**5**.[7] Sulfide (±)-**6** was obtained in excellent yield from the triethylsilyl ether derived from (±)-**5** by treatment with *tert*-butyllithium and diphenyl disulfide in the presence of TMEDA (Scheme 3). Subsequent oxidation to

(5) Evans, D. A.; Gauchet-Prunet, J. A. *J. Org. Chem.* **1993**, *58*, 2446.

(6) Hoppe, D.; Zshage, O. *Angew. Chem., Int. Ed.* **1989**, *28*, 69. Zshage, O.; Hoppe, D. *Tetrahedron* **1992**, *48*, 5657.

(7) Hoppe, D.; Hanko, R.; Brönneke, A.; Lichtenberg, F.; Van Hulsen, E. *Chem. Ber.* **1985**, *118*, 2822.

Scheme 3



the corresponding sulfone was carried out with hydrogen peroxide in the presence of a catalytic amount of ammonium molybdate tetrahydrate. Deprotection of the TES ether gave carbamate sulfone (±)-**7** in 89% yield.

The key conjugate addition proceeded in very good yield and selectivity, affording protected *syn* diol (±)-**8** as a single diastereomer. The diastereoselectivity at the diol level was not unexpected; all the substituents on the 1,3-dioxane ring are equatorial and thus (±)-**8** is the thermodynamically favored product. However, we were surprised to see that the diastereoselectivity was also excellent for the formation of the stereocenter bearing the carbamate and the sulfone groups. The configuration of this carbon has not been determined, since it is destroyed in the next step, but could be exploited by performing a nucleophilic substitution of the sulfone group.

Attempts to hydrolyze the carbamate moiety under acidic conditions failed to produce aldehyde (±)-**9** or the corresponding deprotected lactol (±)-**11**.[8,9] Transformation of the key intermediate into the desired aldehyde was effected in two steps: reduction of the carbamate with $LiAlH_4$[10] produced aldehyde (±)-**9** by elimination of benzenesulfinate,[11] but this aldehyde was subsequently reduced to the primary alcohol in 81% yield. This alcohol could be reoxidized to the desired aldehyde (±)-**9** by *o*-iodoxybenzoic acid (IBX)[12] in 74% yield. Aldehyde (±)-**9** could be transformed into olefin (±)-**10** with phosphorane **2** in 89% yield.[13]

(8) Prolonged exposure to 3 N HCl/THF at 65 °C cleanly gave alcohol **7**.

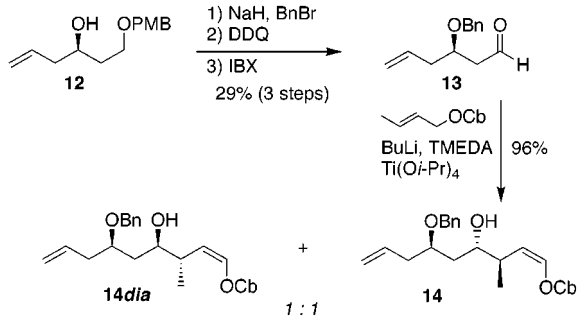
(9) Lactol **11** was also prepared by diasteresoselective epoxidation (73%, >95:5) followed by acidic hydrolysis (74%), according to: (a) Hoppe, D.; Lübmann, J.; Jones, P. G.; Schmidt, D.; Sheldrick, G. M. *Tetrahedron Lett.* **1986**, *27*, 3591. (b) Hoppe, D.; Tarara, G.; Wilckens, M. *Synthesis* **1989**, 83.

(10) Hoppe, D.; Tebben, P.; Reggelin, M.; Bolte, M. *Synthesis* **1997**, 183.

(11) For a similar elimination, see ref 9.

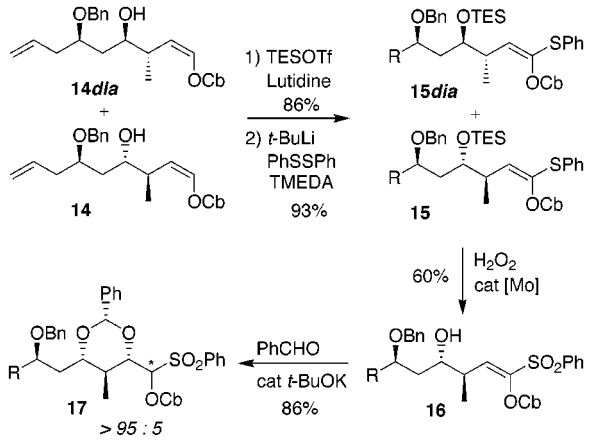
Having in hand a route to a model compound of the C16−C24 fragment of Dolabelides, we addressed the synthesis of this fragment. Aldehyde **13** was prepared in 3 steps from known alcohol **12** (Scheme 4).[14] The required carbamate was

Scheme 4



obtained as a 1:1 inseparable mixture of diastereomers **14** and **14*dia*** by performing a Hoppe homoaldol with TMEDA at 0 °C.[15] Fortunately, sulfides **15** and **15*dia*** were separable by flash chromatography (Scheme 5). Oxidation to the sulfone was accompanied by TES deprotection if hydrogen

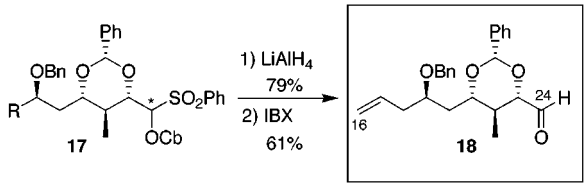
Scheme 5



peroxide was used in excess. The key step again proceeded with excellent diastereoselectivity to furnish **17** in 86% yield.

Conversion of **17** to the required aldehyde **18** was uneventful (Scheme 6), and the C16−C24 fragment of Dolabelides was obtained in two steps: $LiAlH_4$ reduction (79%), followed by IBX oxidation (61%).

Scheme 6



In conclusion, we have designed a new method to make synthons encompassing a protected *syn* 1,3-diol motif and an aldehyde α to the 1,3-dioxane ring. Moreover, an additional stereocenter is created during this sequence, potentially leading to stereochemically defined 1,2,4-triols. This methodology was successfully applied to the synthesis of the C16−C24 portion of Dolabelides.

Acknowledgment. We gratefully acknowledge the CNRS (UMR 7652) and the Ecole Polytechnique for financial support. Wilfried Nassiet, Marion Kopec, and Claire Thoumazet are thanked for preliminary experiments.

Supporting Information Available: Experimental procedures and full characterization for compounds **6**−**9** and **15**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL017122W

(12) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019. Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272.

(13) Lactol **11** was also converted to compound **10** by Wittig coupling with phosphorane **2** (95%), followed by protection of the resulting diol (52%).

(14) Wu, Y.; Esser, L.; De Brabander, J. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 4308.

(15) Kinetic resolution with 2 equiv of the crotyl carbamate at −78 °C (according to Berque, I.; Le Ménez, P.; Razon, P.; Anies, C.; Pancrazi, A.; Ardisson, J.; Neuman, A.; Prangé, T.; Brion, J.-D. *Synlett* **1998**, 1132) produced a 1.5:1 mixture of diastereomers favoring the undesired **14*dia***.