ORGANIC LETTERS

2000
Vol. 2, No. 7
993−996

A New, More Efficient, and Effective Process for the Synthesis of a Key Pentacyclic Intermediate for Production of Ecteinascidin and Phthalascidin Antitumor Agents

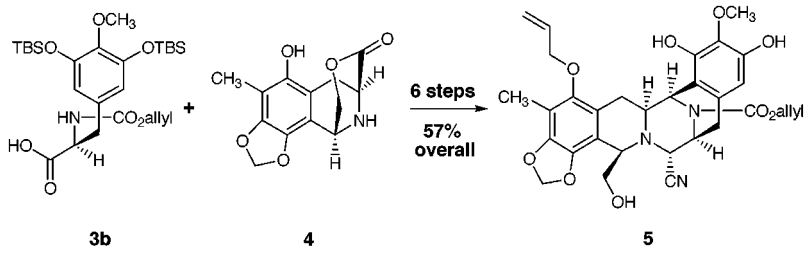
Eduardo J. Martinez and E. J. Corey*

Department of Chemistry and Chemical Biology Harvard University, 12 Oxford Street, Cambridge, Massachusetts 02138

corey@chemistry.harvard.edu

Received February 15, 2000

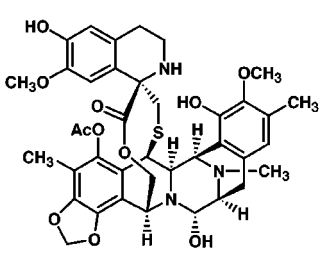
ABSTRACT



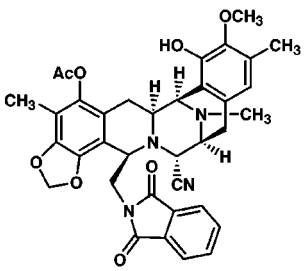
3b 4 5

An efficient process is described for the synthesis of 5, a key intermediate for the synthesis of the potent antitumor agents ecteinascidin 743 (1) and phthalascidin (2) from the readily available building blocks 3b and 4.

Ecteinascidin 743 (**1**, Et 743) is an exceedingly potent marine-derived antitumor agent[1] which is now being studied in various clinics with human patients.[2] Because this



1



2

compound is not sufficiently available from the natural source, the tunicate *Ecteinascidia turbinate*, it is being produced industrially by the totally synthetic route described in 1996.[3] More recently, a structural analogue of Et 743, compound **2** (phthalascidin, Pt 650), has been found to exhibit antitumor activity essentially indistinguishable from that of **1**.[4] Both **1** and **2** are synthesized from building blocks

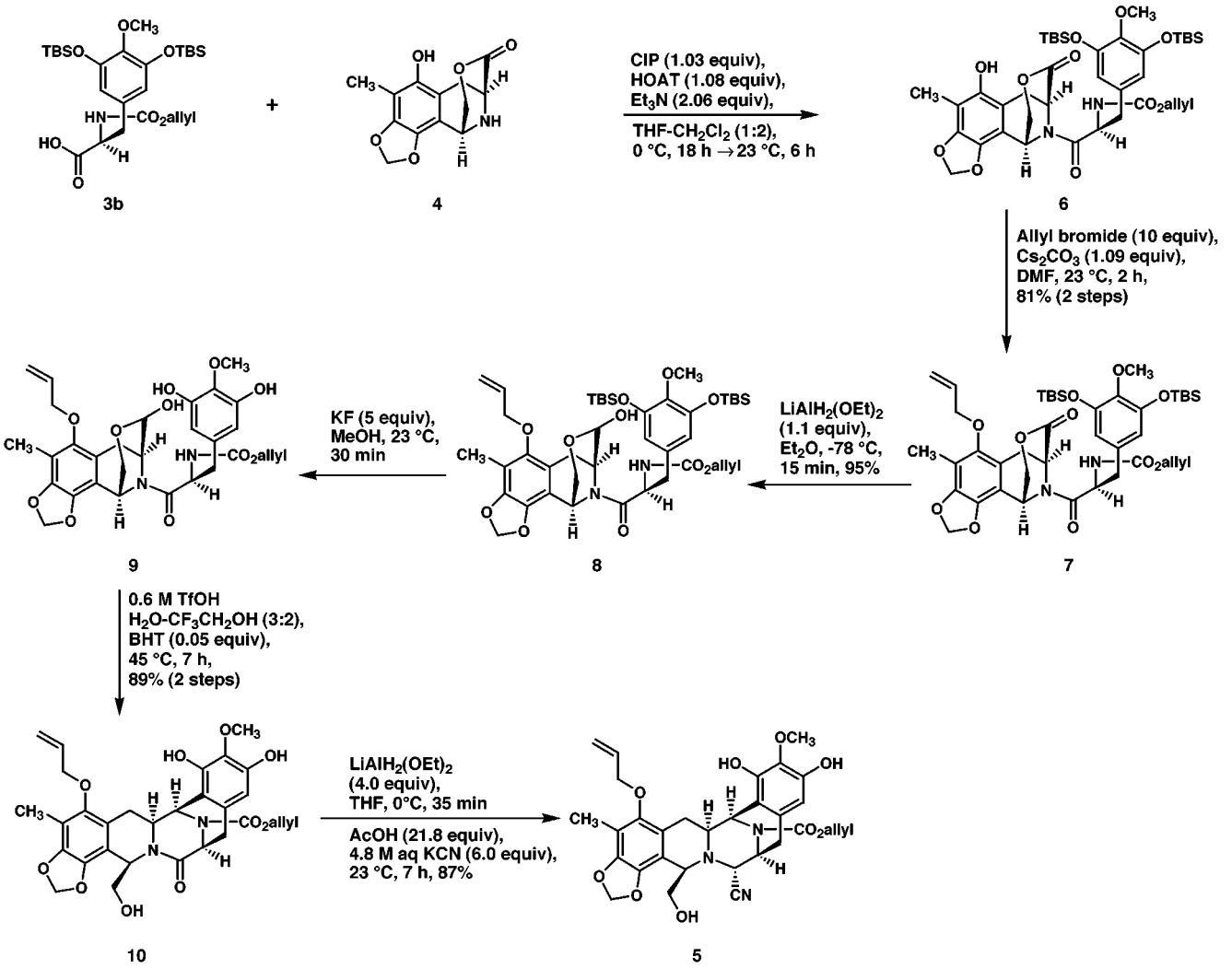
(1) The pioneering research in this area is due to Prof. Kenneth L. Rinehart and his group. See: (a) Rinehart, K. L.; Shield, L. S. In *Topics in Pharmaceutical Sciences*; Breimer, D. D., Crommelin, D. J. A., Midha, K. K., Ed.; Amsterdam Medical Press: Noordwijk, The Netherlands, 1989; p 613. (b) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Keifer, P. A.; Wilson, G. R.; Perun, T. J., Jr.; Sakai, R.; Thompson, A. G.; Stroh, J. G.; Shield, L. S.; Seigler, D. S.; Li, L. H.; Martin, D. G.; Grimmelikhuijzen, C. J. P.; Gäde, G. *J. Nat. Prod.* **1990**, *53*, 771. (c) Rinehart, K. L.; Sakai, R.; Holt, T. G.; Fregeau, N. L.; Perun, T. J., Jr.; Seigler, D. S.; Wilson, G. R.; Shield, L. S. *Pure Appl. Chem.* **1990**, *62*, 1277. (d) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Stroh, J. G.; Keifer, P. A.; Sun, F.; Li, L. H.; Martin, D. G. *J. Org. Chem.* **1990**, *55*, 4512. (e) Wright, A. E.; Forleo, D. A.; Gunawardana, G. P.; Gunasekera, S. P.; Koehn, F. E.; McConnell, O. J. *J. Org. Chem.* **1990**, *55*, 4508. (f) Sakai, R.; Rinehart, K. L.; Guan, Y.; Wang, H.-J. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 11456.

(2) (a) *Business Week* September 13, **1999**, 22. (b) *Science* **1994**, *266*, 1324.

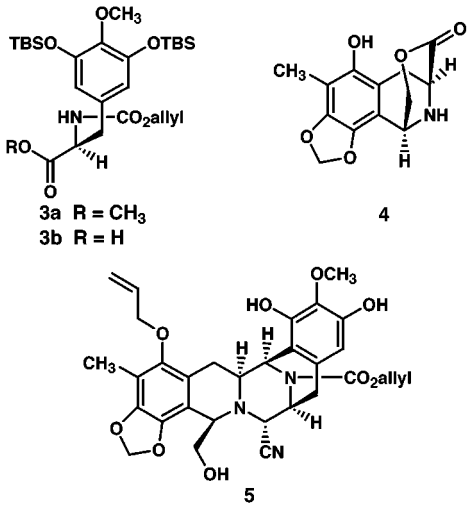
(3) Corey, E. J.; Gin, D. Y.; Kania, R. *J. Am. Chem. Soc.* **1996**, *118*, 9202.

10.1021/ol0056729 CCC: $19.00
Published on Web 03/15/2000

Scheme 1



3 and **4** via a common pentacyclic intermediate, **5**. The synthesis of **5** was accomplished originally[3] from building blocks **3a** and **4** in six steps with an overall yield of 35% (average yield per step of ca. 84%). Because the industrial syntheses of **1** and/or **2** would eventually have to be produced economically on a multikilogram scale, we sought to find a more efficient and reproducible alternative route from **3** and **4** to **5**. Reported herein is a new process which is simpler to carry out than the original and which proceeds from **3b** + **4** to **5** in six steps with an overall yield of 57% (average yield per step of nearly 92%). The pathway of synthesis of pentacycle **5** is summarized in Scheme 1.[5]

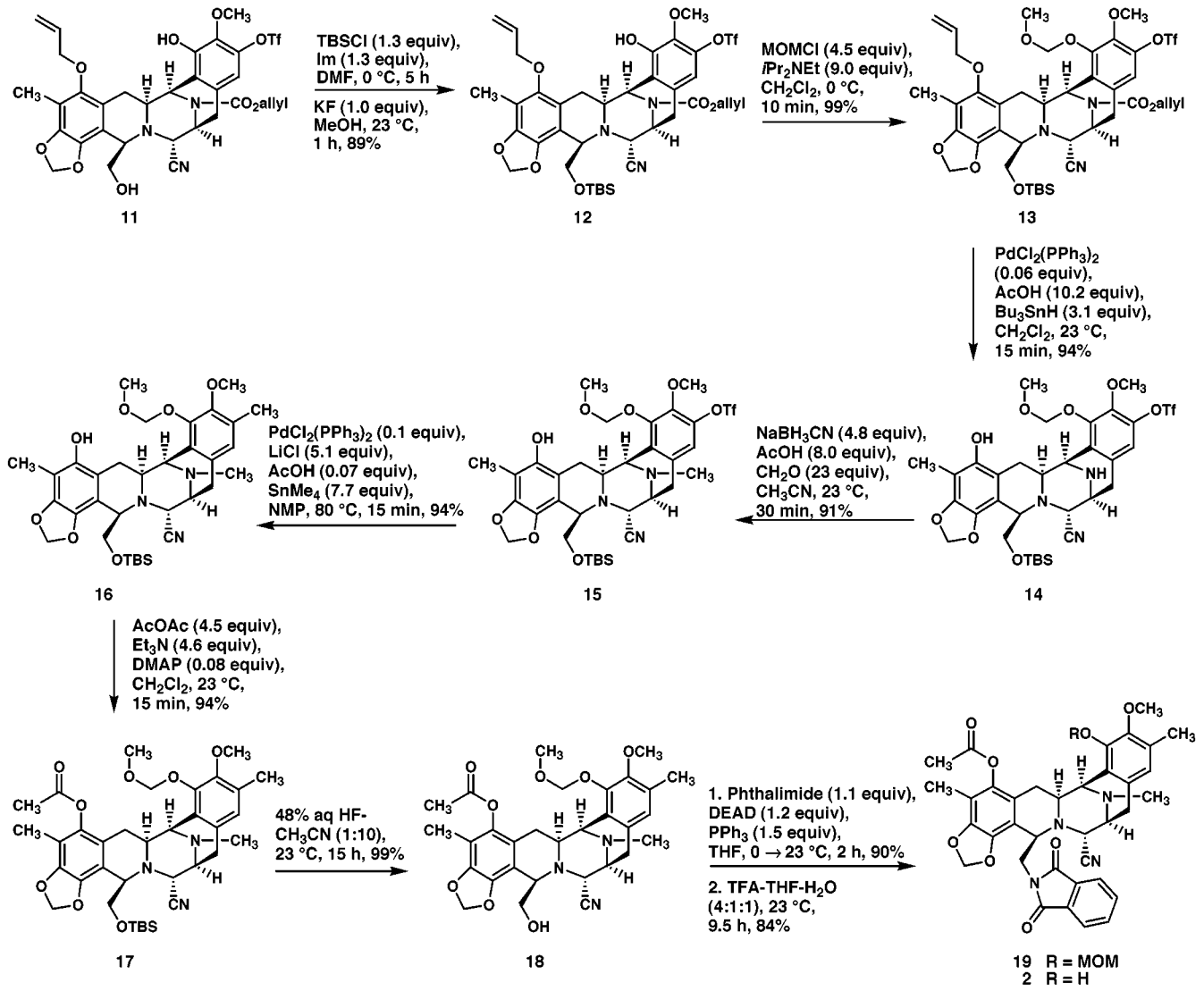


A solution of azeotropically dried (C_7H_8−THF) amino lactone **4**[3] in THF at 0 °C was treated dropwise with an acylating reagent prepared from acid **3b**[3] (1.03 equiv), 1-hydroxy-7-azabenzotriazole (HOAT, 1.08 equiv), 2-chloro-1,3-dimethylimidazolidinium hexafluorophosphate (CIP, 1.03 equiv), and triethylamine (2.06 equiv) in CH_2Cl_2 solution at 0 °C.[6] The coupling product **6**, which was obtained by extractive workup, was allylated without further purification by treatment in DMF solution at 23 °C with excess allyl

(4) Martinez, E. J.; Owa, T.; Schreiber, S. L.; Corey, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 3496.

(5) See: Myers, A. G.; Kung, D. W. *J. Am. Chem. Soc.* **1999**, *121*, 10828 for a different approach to the synthesis of structures such as **5**.

Scheme 2



bromide and 1.09 equiv of Cs_2CO_3 to give amide **7** in 81% overall yield from **3a** and **4** after flash chromatography on silica gel. Selective reduction of the lactone function of **7** to the corresponding lactol (**8**) was effected by reaction with 1.1 equiv of lithium diethoxyaluminum hydride ($LiAlH_2(OEt)_2$) in ether at −78 °C for 15 min in 95% yield.[7,8] Desilylation of **8** to **9** and cyclization of **9** (without purification) using 0.6 M triflic acid in 3:2 $H_2O-CF_3CH_2OH$ at 45 °C for 7 h produced pentacyclic product **10** in 89% overall yield from **8**. Finally, the lactam function of **10** could be reduced cleanly by treatment with 4 equiv of $LiAlH_2(OEt)_2$ in THF at 0 °C for 35 min to the corresponding cyclic aminal which upon exposure to HCN provided pentacyclic amino nitrile **5** in 87% overall yield from **10** after flash chromatography on silica gel.[9]

The synthesis of **5** which is outlined in Scheme 1 and described above is advantageous relative to the originally used synthetic pathway[3] not only because of the substantially greater overall yield (57 vs 35%) but also because of the simplicity and reproducibility of the individual steps, especially the amide coupling (**3b** + **4** → **6**) and the internal Pictet−Spengler cyclization (**9** → **10**). In addition, no difficulties have been encountered either in product purification or scale-up. A critical element to the success of the

(6) For carboxylic acid−amine coupling methodology using CIP, see: (a) Akaji, K.; Kuriyama, N.; Kimura, T.; Fujiwara, Y.; Kiso, Y. *Tetrahedron Lett.* **1992**, *33*, 3177. (b) Akaji, K.; Kuriyama, N.; Kiso, Y. *Tetrahedron Lett.* **1994**, *35*, 3315. (c) Akaji, K.; Kuriyama, N.; Kiso, Y. *J. Org. Chem.* **1996**, *61*, 3350.

(7) The reagent $LiAlH_2(OEt)_2$ was prepared by the addition of 1 equiv of ethyl acetate to a solution of $LiAlH_4$ in ether solvent at 0 °C and stirring at 0 °C for 2 h just before use; see: Brown, H. C.; Tsukamoto, A. *J. Am. Chem. Soc.* **1964**, *86*, 1089.

(8) For general reviews on the reduction of lactones, see: (a) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567. (b) Cha, J. S. *Org. Prep. Proc. Int.* **1989**, *21(4)*, 451. (c) Seyden-Penne, J. *Reduction by the Alumino- and Borohydrides in Organic Synthesis*, 2nd ed.; Wiley-VCH: New York, 1997; Section 3.2.5.

(9) For general references on amide reduction by hydride reagents, see ref 7 and also the following: Myers, A. G.; Yang, B. H.; Chen, H.; Gleason, J. L. *J. Am. Chem. Soc.* **1994**, *116*, 9361.

sequence shown in Scheme 1 was the high efficiency and selectivity of $LiAlH_2(OEt)_2$ for the two reduction steps **7** → **8** and **10** → **5**, which suggest that this reagent can be used to advantage in synthesis much more frequently than it has been previously. In this connection it is noteworthy that the use of diisobutylaluminum hydride in C_7H_8 and triisobutylaluminum in Et_2O for the reduction of **7** produced **8** in yields of only 41% and 73%, respectively.

The synthetic route from **5** to phthalascidin **2**, which proceeds smoothly and in excellent yield (average yield per step 90.8%), is outlined in Scheme 2. Pentacyclic triol **5** was converted to phenolic monotriflate **11** by treatment with 1.1 equiv of $PhNTf_2$ (McMurry reagent), 2 equiv of Et_3N, and 0.2 equiv of 4-(dimethylamino)pyridine in CH_2Cl_2 at −30 °C for 38 h (74%). Conversion of **11** to mono *tert*-butyldimethylsilyl (TBS) ether **12** and etherification with methoxymethyl chloride (MOMCl) produced **13** in high yield. Cleavage of the *N*-allyloxycarbonyl and *O*-allyl groups in **13** gave secondary amine **14** (94%) which was *N*-methylated to **15** and C-methylated to **16**. Acetylation of phenol **16** produced the corresponding acetate **17** which upon desilylation formed primary alcohol **18**. Mitsunobu displacement of the primary hydroxyl of **18** produced phthalimide **19** which upon acid-catalyzed cleavage of the methoxymethyl ether provided pure phthalascidin **2**.

Since the original synthetic route to Et 743 (**1**) has proved to be acceptable for large scale synthesis, it is our expectation that the improved process described herein will be even more useful, as will the new route to phthalascidin (**2**).[4] Because phthalascidin is more stable than ecteinascidin 743 and considerably easier to make, it may prove to be a more practical therapeutic agent.

Acknowledgment. This research was assisted financially by grants from Pfizer Inc. and the National Institutes of Health and a graduate fellowship to E.M. from the Schering Plough Corporation. Early work in these laboratories on the application of $LiAlH_2(OEt)_2$ to the selective reduction of lactams to cyclic aminals was carried out by Dr. Victor Behar, to whom we are most grateful.

OL0056729