Natural Products

DOI: 10.1002/anie.200503983

Stereospecific Formal Total Synthesis of Ecteinascidin 743**

*Shengping Zheng, Collin Chan, Takeshi Furuuchi, Benjamin J. D. Wright, Bishan Zhou, Jinsong Guo, and Samuel J. Danishefsky**

Dedicated to Professor Ryoji Noyori

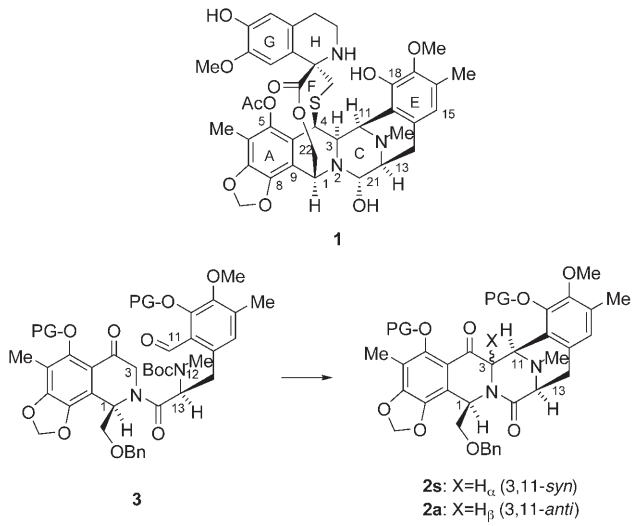
In the preceding communication in this issue, we described a comprehensive study directed at understanding the multifaceted stereochemical issues associated with the cascadelike reaction initiated by cleavage of the urethane function of an *N*-methyl-*N*-Boc ketoaldehyde of the type **3**.[1] Even after extensive experimentation, we could not realize a lynchpin Mannich cyclization of the type **3**→**2s** (**s** = *syn*). Such a cyclization, had it occurred, would have found ready application in the total synthesis of the highly cytotoxic natural product ecteinascidin 743 (**1**; Scheme 1).[2] In practice, it was shown with C1 and C13 matched in their correct relative and absolute configurations as shown in **3** that the product is cleanly the 3,11-*anti* compound **2a** (**a** = *anti*). At no time could we pass from a **2a** to a **2s** compound by epimerization at C3.[3] To attain the relative and absolute stereochemistry at C3, C11, and C13 required to reach **1**, it would be necessary to resort to mismatching at C1 (i.e. (*S*)-C1 rather than (*R*)-C1 configuration). This would in turn necessitate a late-stage and problematic epimerization at C1.[4] In summary, at no stage could we solve the ecteinascidin 743 problem (encompassing C1, C3, C4, C11, and C13) or the saframycin total synthesis problem (encompassing C1, C3, C11, and C13) by direct cyclization of appropriately matched ((*R*)-C1, (*S*)-C13) precursors bearing ketone and aldehyde functions at C4 and C11, respectively (cf. **3**).[5]

[*] Dr. S. Zheng, C. Chan, Dr. T. Furuuchi, B. J. D. Wright, Dr. B. Zhou, Dr. J. Guo, Prof. S. J. Danishefsky
The Department of Chemistry
Columbia University
Havemeyer Hall, New York, NY 10027 (USA)
Fax: (+1) 212-772-8691
E-mail: s-danishefsky@ski.mskcc.org
Prof. S. J. Danishefsky
The Laboratory for Bioorganic Chemistry
Sloan-Kettering Institute for Cancer Research
1275 York Avenue, New York, NY 10021 (USA)

[**] This work was supported by the National Institutes of Health (Grant HL25848) and by Pharmamar Corporation of Madrid, Spain. We thank Dr. Atsushi Endo for many helpful dicussions. B.J.D.W. gratefully acknowledges the NSF for a predoctoral fellowship. We thank Bristol Myers Squibb for the generous fellowship awarded to C.C. We also thank Dr. Yasuhiro Itagaki (Columbia University) for mass spectrometric analyses

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

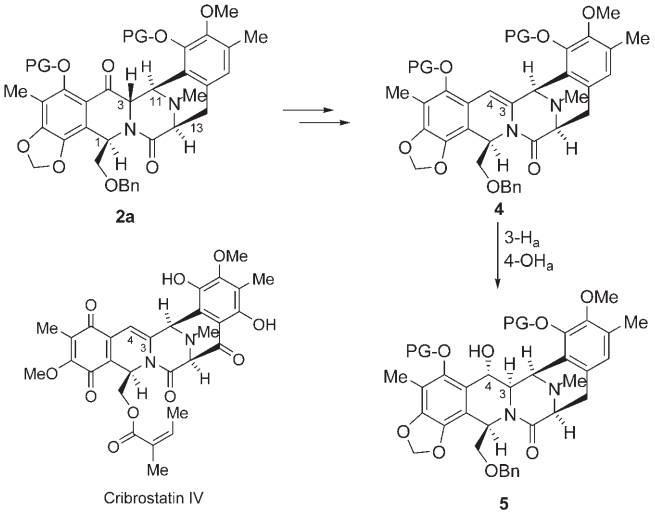
WILEY InterScience DISCOVER SOMETHING GREAT
© 2006 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 1. Lynchpin Mannich strategy en route to ecteinascidin 743 (**1**). PG = protecting group.

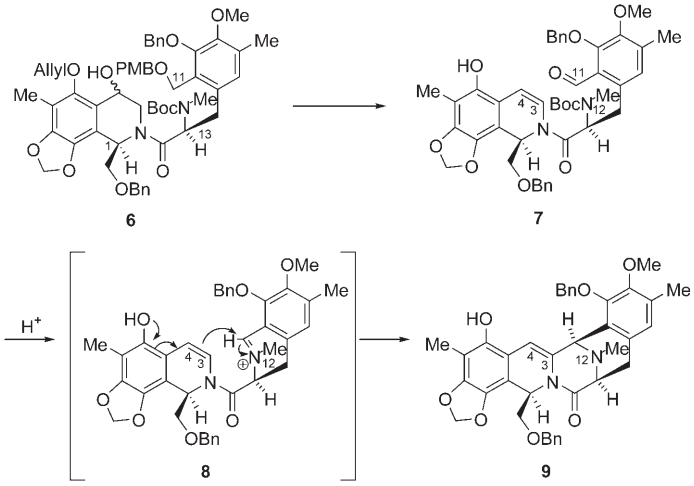
Previously, in connection with our total synthesis of cribrostatin IV, we charted a viable pathway from a **2a**-type compound to a 3,4-dehydro-type compound (cf. **4**).[6] Of course, in cribrostatin IV, the final target we were pursuing contains a 3,4-olefinic linkage. Accordingly, we envisioned an indirect solution to the ecteinascidin 743/saframycin total synthesis problem by reaching a **2a** species that would be converted into a 3,4-dehydro system (cf. **4**).[7] We hoped to reach a key intermediate (cf. **5**) required for the ecteinascidin 743 series from **4** through an overall α-face hydration (i.e. 3-H_α, 4-OH_α) of the C3–C4 double bond (see **5**, Scheme 2).

On further reflection, a conceptually simpler possibility presented itself. Perhaps direct cyclization of an *ortho*-hydroxystyrene prototype **7** would occur at the styrene double bond, with its regiochemical sense controlled by the hydroxy group of the phenol moiety. The cyclization we envisioned (presumably via the iminium derivative **8**, formed upon cleavage of the Boc group from N12) would produce **9**



Scheme 2. Proposed epimerization strategy at C3.

(Scheme 3). Given the importance of providing access to a broad range of biologically active tetrahydroisoquinoline alkaloids, it seemed prudent to gain reliable and convenient access to the required matched antipodes.[8] Indeed, as will be



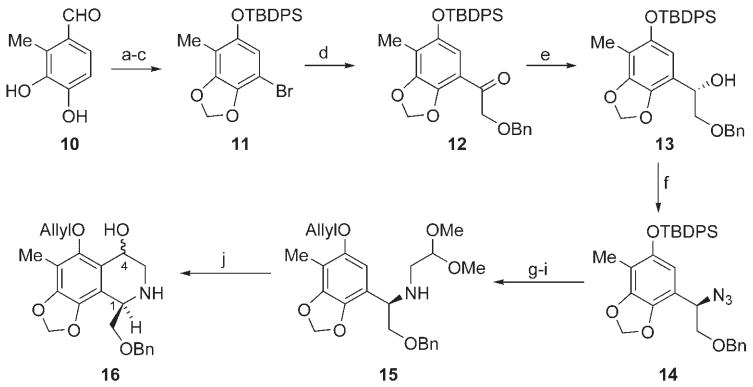
Scheme 3. Construction of the pentacycle through a novel vinylogous Pictet–Spengler cyclization.

described, a new concise plan was devised to reach the configurationally defined tetrahydroisoquinoline moiety ((*R*)-C1). The latter was acylated with the enantiomerically defined L-aminoacyl CDE precursor, bearing the future C11 aldehyde (see compound **6**).[9]

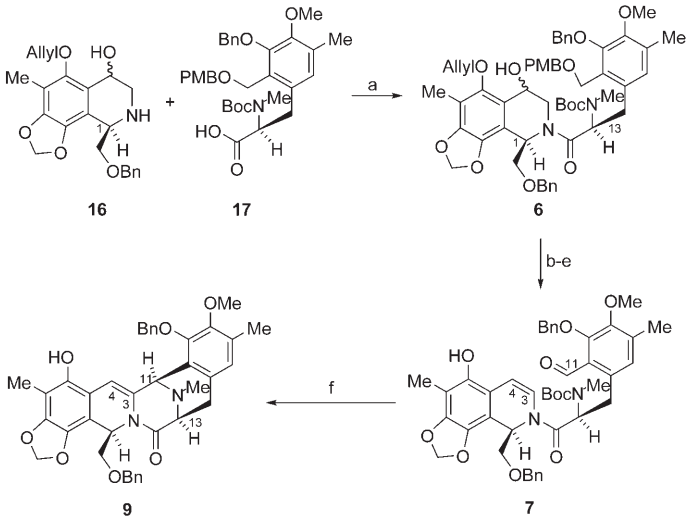
Our synthesis started with a highly regiospecific bromination of the Borchardt catechol **10** (Scheme 4).[10] Engagement of the catechol hydroxyl groups (by methylenation) set the stage for successful Baeyer–Villiger oxidation and hydrolysis. The resultant phenol was protected as its *tert*-butyldiphenylsilyl ether **11**. Lithiation of the bromine function followed by coupling of the organometallic agent with the Weinreb amide of benzyloxyglycolic acid yielded **12**.[11] Asymmetry was introduced by submitting ketone **12** to Noyori transfer-hydrogenation conditions, thereby providing homochiral **13**.[12] A modified Mitsunobu reaction of alcohol **13** with diphenylphosphorylazide gave rise to **14**, with complete inversion of stereochemistry.[13] At this stage, the *R* configuration at C1 was securely fashioned. Catalytic hydrogenation of **14** to the amine was followed by two-carbon-atom homologation, and subsequent deprotection/reprotection of the phenol as its allyl ether gave acetal **15**. The Bobbitt-modified Pomerantz–Fritsch reaction of **15** provided the required tetrahydroisoquinoline **16**, in which the stereochemistry at C1 was correctly defined.[14] That C4 is, at this stage, presented as a mixture of epimers, is an awkwardness rather than an impediment (see below).

Coupling of tetrahydroisoquinoline **16** and the previously described L-tyrosine derivative **17**[6] under the agency of BOPCl afforded amide **6** in excellent yield (Scheme 5). After oxidative cleavage of the PMB group and dehydration of the benzylic alcohol,[15] the primary alcohol was oxidized to the C11 aldehyde.[16] The allyl group was cleaved by treatment with tributyltin hydride in the presence of catalytic

 © 2006 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



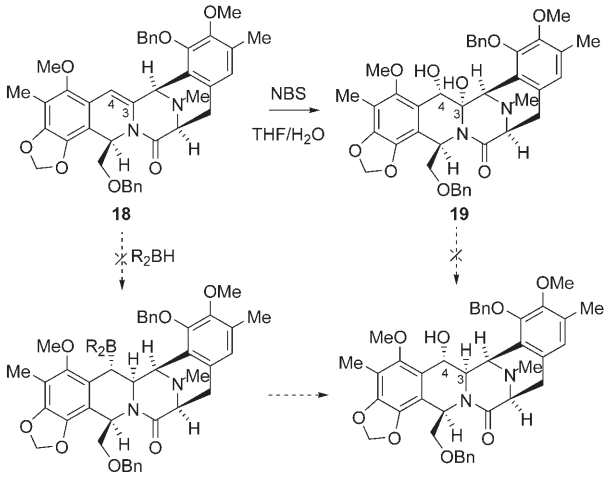
Scheme 4. a) 1) Br_2 (1.01 equiv), NaOAc (1.05 equiv), AcOH, 0 °C→25 °C, 12 h; 2) $BrCH_2Cl$ (1.5 equiv), Cs_2CO_3 (1.5 equiv), DMF, 105 °C, 12 h, 66%; b) 1) MCPBA (3 equiv), 25 °C→64 °C, 3 h; 2) HCl (0.3 equiv), 0 °C→25 °C, 12 h, 78%; c) TBDPSCl (1.15 equiv), TEA (1.5 equiv), DMAP (0.1 equiv), 25 °C, 12 h, 89%; d) 1) *n*BuLi (1.6 M; 1.1 equiv), toluene/THF (9:1), −78 °C, 20 min; 2) neat Me-(MeO)NC(O)CH_2OBn (1.5 equiv), −78 °C, 50 min, 80%; e) Noyori *R,R* catalyst (0.01 equiv), HCO_2H (13.2 equiv), TEA (7.8 equiv), DMF, 0 °C→40 °C, 24 h, 78% (95% *ee*); f) DPPA (2 equiv), DBU (2 equiv), toluene/DMF (9:1), 50 °C, 24 h, 89% (95% *ee*); g) H_2 (1 atm), Pd/C (5%), EtOAc, 25 °C, 15 h, 80%; h) 1) $(MeO)_2CHCHO$ (1 equiv), AcOH (4 equiv), $NaCNBH_3$ (1.3 equiv), $MgSO_4$ (6 equiv), MeOH, 0 °C→65 °C, 4 h; 2) TBAF (1.5 equiv), THF, 0 °C, 30 min, 94%; i) allyl bromide (1.15 equiv), NaH (2.8 equiv), DMF, 0 °C→25 °C, 2 h, 84%; j) 7 M HCl (70 equiv), dioxane, 0 °C→25 °C, 72 h, 90%. DMF = *N,N*-dimethylformamide; MCPBA = *m*-chloroperoxybenzoic acid; TBDPS = *tert*-butyldiphenylsilyl; TEA = triethylamine; DMAP = 4-(dimethylamino)pyridine; Bn = benzyl; DPPA = diphenylphosphoryl azide; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; TBAF = tetrabutylammonium fluoride.



Scheme 5. a) BOPCl (1.1 equiv), TEA (3 equiv), CH_2Cl_2, 0 °C→25 °C, 24 h, 85%; b) DDQ (1.6 equiv), CH_2Cl_2/pH 7.00 buffer solution (18:1), 25 °C, 30 min, 90%; c) $Cu(OTf)_2$ (0.2 equiv), benzene, 85 °C, 15 min, 61%; d) DMP (1.5 equiv), CH_2Cl_2, 25 °C, 5 h, 94%; e) $[(PPh_3)_2PdCl_2]$ (0.2 equiv), Bu_3SnH (1.2 equiv), AcOH (5 equiv), 0 °C→25 °C, 1 h, 93%; f) CHF_2CO_2H (30 equiv), $MgSO_4$ (4 equiv), benzene, 100 °C, 45 min, 42–58%. BOPCl = bis(2-oxo-3-oxazolidinyl)phosphinic chloride; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DMP = Dess–Martin periodinane.

$[(Ph_3P)_2PdCl_2]$ to yield cyclization precursor **7**, as hypothesized above.[17] The resulting aldehyde **7** was suited for the crucial intramolecular Pictet–Spengler cyclization. We screened various acidic conditions for achieving the desired cyclization to **9**. In the event, compound **7** successfully underwent cyclization to produce pentacycle **9** upon exposure to 30 equivalents of difluoroacetic acid in benzene. For the moment, the product is obtained in a somewhat disappointing yield of 42–58%.

With a viable route to pentacyclic alkene **9** in hand, we were now faced with the need to functionalize the C3–C4 double bond (Scheme 6). Implementation of this task



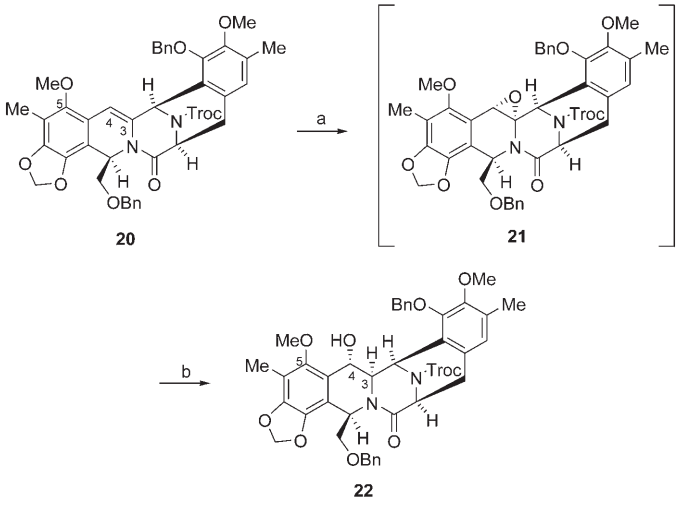
Scheme 6. Unsuccessful attempts to refunctionalize the C3–C4 olefinic linkage. NBS = *N*-bromosuccinimide.

commenced with temporary protection of phenol **9** as its methyl ether derivative **18**. As **18** could be readily obtained in ample quantities, it was used as a model to probe eventual management of the synthesis in a fully updated system. In our first attempts to functionalize the C3–C4 double bond, we took recourse to hydroboration reagents such as BTHF, BMS, BH_3·Py, Br_2BH, and catecholborane. Remarkably, such attempts uniformly resulted only in recovery of **18**.[18] By contrast, the double bond of **18** could be dihydroxylated with *N*-bromosuccinimide in aqueous THF, leading to a diol assigned as **19** in which the dihydroxylation was presumed to occur from the less-hindered α face.[19] However, attempted reductive removal of the now extraneous angular 3-OH group of **19** with a variety of reducing agents resulted in the recovery of starting material.

Given these results, we concluded that to be successful, a highly reactive oxidizing agent would be needed to attack the double bond. We also needed functionality at C3, which would be more reactive than a simple hydroxy group to allow introduction of the required 3-H_α group. Accordingly, we first explored the use of peracid agents for the epoxidation of the C3–C4 olefin linkage. However, at this stage *N*-oxide formation of the N–Me tertiary amine group became a potential problem. Accordingly, we conducted a McCluskey reaction to afford *N*-Troc urethane **20**.[20] Unfortunately, attempts at various epoxidizing conditions with peracids were unsuccessful (possibly owing to the slowness of the desired reaction in the context of the highly oxidizable aromatic sectors). With our options rapidly narrowing, it was fortunate

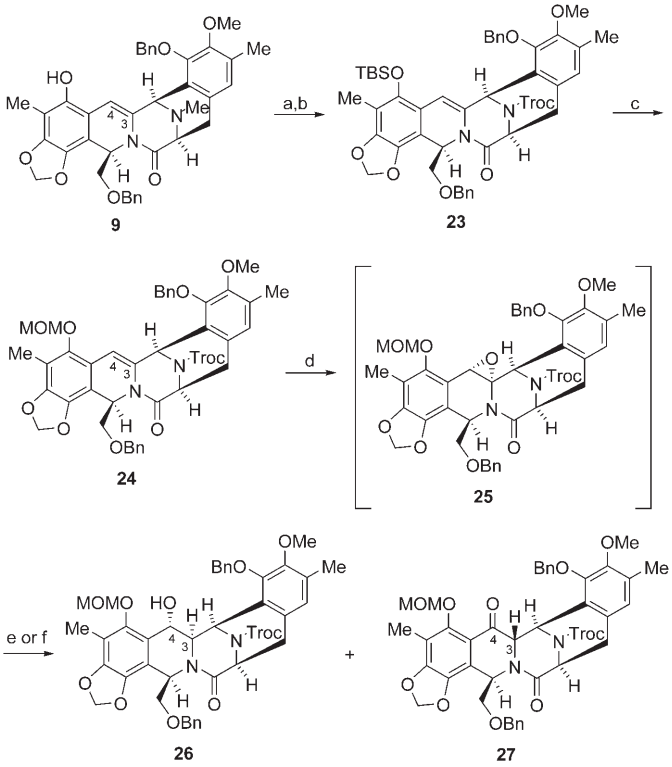
 © 2006 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

that reaction of **20** with 2,2-dimethyldioxirane (DMDO) did occur, giving rise to material formulated as the C3–C4 α-epoxide **21** (Scheme 7).[2d] Treatment of **21** with sodium cyanoborohydride provided the required 3-H_α, 4-OH_α hydration product **22**. Greater insight into this fascinating reductive cleavage of the novel enamide epoxide (*cf.* **21**) was gained in the MOM ether series (see below, compound **25**).

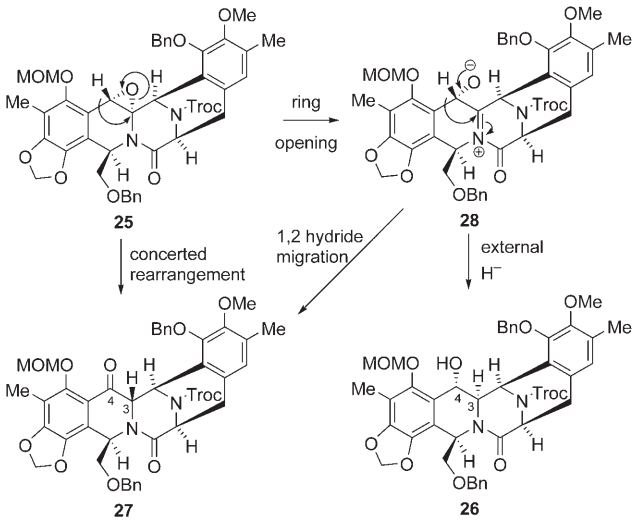


Scheme 7. a) DMDO (1.5 equiv), CH_2Cl_2, 0 °C→25 °C, 30 min; b) $NaCNBH_3$ (5 equiv), 10 min, 75 %. DMDO = dimethyl dioxirane.

On the basis of our experiences in this series, we could not be confident that a compound such as **22**, containing a methyl ether at C5 could be advanced to conclude the synthesis. Moreover, in the same vein, it was decided to confirm our various assignments by connecting our series with a previously synthesized intermediate, from which ecteinascidin 743 could definitely be reached. Accordingly, we defined **32** as our milestone target, which is an advanced intermediate in the Fukuyama total synthesis of ecteinascidin 743.[2d] Phenol **9** was first converted into its *tert*-butyldimethylsilyl ether derivative (Scheme 8). This step was followed by a McCluskey reaction of the N–Me amine, thereby providing **23**. Deprotection of the TBS ether with TBAF, followed by addition of MOMCl and Hünig base, led to **24** in good yield.[21] Treatment of this compound with DMDO led, as before (cf. **20**), to epoxidation of the C3–C4 double bond, thus affording the presumed **25**. When this compound was treated with 5 equivalents of sodium cyanoborohydride the major product obtained was a ketone assigned as shown in **27**, although small amounts of **26** were also obtained. Two mechanistic hypotheses were entertained to account for the formation of the ketone (Scheme 9). One could envision a concerted rearrangement with hydride migration, from C4 to C3, to afford ketone **27**. Alternatively, the nitrogen atom of the lactam opens the epoxide to produce amidonium alkoxide **28**. This intermediate can undergo 1,2-hydride migration to give **27** or competitive reduction by an external hydride to provide **26**. Apparently this duality is, in fact, operative, since recourse to a large excess of sodium cyanoborohydride does afford **26** as the predominant product.[22]



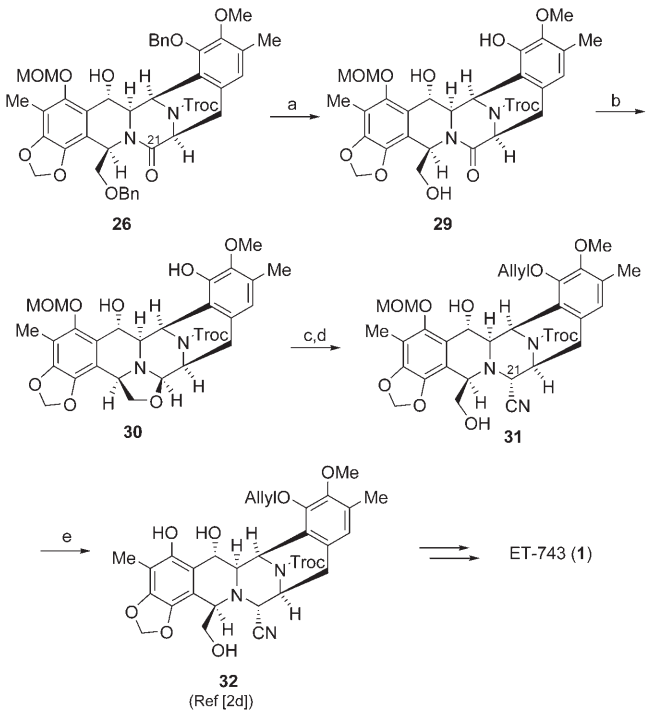
Scheme 8. a) TBSOTf (2.5 equiv), TEA (3 equiv), CH_2Cl_2, 0 °C, 30 min, 100 %; b) TrocCl (20 equiv), TBAI (3 equiv), toluene, 110 °C, 3 h, 92 %; c) 1) TBAF (3 equiv), CH_2Cl_2, 0 °C, 2 min; 2) MOMCl (3 equiv), Hünig base (5 equiv), 30 min, 79 %; d) DMDO (2 equiv), CH_2Cl_2, 0 °C→25 °C, 1.5 h; e) $NaCNBH_3$ (5 equiv), 10 min, **27**/**26** 60 %:10 %; f) $NaCNBH_3$ (50 equiv), 10 min, (**26**) 78 %. TBS = *tert*-butyldimethylsilyl; Tf = trifluoromethanesulfonyl; Troc = 2,2,2-trichloroethoxycarbonyl; TBAI = tetrabutylammonium iodide; MOM = methoxymethyl.



Scheme 9. Mechanistic proposals for the reduction of epoxide **25** to alcohol **26** and ketone **27**.

At this juncture, we faced only the installation of the cyano function at C21 (Scheme 10). Toward this end, the two benzyl protecting groups were removed, thereby giving rise to

 © 2006 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



Scheme 10. a) H_2 (1 atm), Pd/C (10%), EtOAc, 25°C, 3 h, 77%; b) DIBAL-H/BuLi (1:1; 40 equiv), THF, 0°C, 5 h, 78%; c) allyl bromide (20 equiv), Hünig base (25 equiv), CH_2Cl_2, 50°C, 16 h, 66%; d) KCN (9 equiv), AcOH, 25°C, 4 h, 79%; e) TFA (1 equiv), CH_2Cl_2, −20°C, 30 min, 54%. DIBAL-H = diisobutylaluminum hydride; TFA = trifluoroacetic acid.

triol **29**. The latter, upon treatment with a 1:1 ate complex of BuLi and DIBAL-H,[23] underwent partial reduction of the lactam to provide oxazolidine **30**. The reduction seemed to be highly dependent on the reactivity of the ate complex, which may differ from batch to batch. It was found that if there was a slight excess of "BuLi" in the ate complex, the Troc protecting group was easily reduced.[24] Fortunately, the phenol hydroxy group was selectively protected as its allyl ether by treatment of oxazolidine **30** with allyl bromide in the presence of Hünig base. Upon exposure to KCN in acetic acid, **30** underwent ring opening and simultaneous introduction of the C21 cyano group to give aminonitrile **31** as a single isomer. The MOM group was cleaved by treatment of **31** with TFA to give the goal compound **32**. As this compound is an advanced intermediate in the Fukuyama total synthesis of **1**,[2d] our work described herein constitutes a formal total synthesis of ecteinascidin 743.

Having validated our routes, we are now in a position to redirect our focus to reaching ecteinascidin 743 by novel and far more concise pathways without necessarily intersecting an existing pathway. We note that several fascinating pieces of chemistry have been developed herein: 1) the very straightforward routes to the matched subunits **16** and **17**, 2) the use of an unusual *o*-hydroxystyrene moiety for the vinylogous Pictet–Spengler cyclization, and 3) exploitation of an unusual enamide epoxide for the hydration of the C3–C4 double bond, in the desired sense, through reductive treatment of **25**. We are currently exploring direct syntheses of ecteinascidin 743 which are enabled by the formal total synthesis described above.

Received: November 9, 2005

Keywords: antitumor agents · asymmetric synthesis · natural products · Pictet–Spengler reaction · total synthesis

[1] See the previous Communication in this issue: C. Chan, S. Zheng, B. Zhou, J. Guo, R. M. Heid, S. J. Danishefsky, *Angew. Chem.* **2006**, *118*, 1781; *Angew. Chem. Int. Ed.* **2006**, *45*, 1749.
[2] Isolation of **1**: a) K. L. Rinehart, T. G. Holt, N. L. Fregeau, J. G. Stroh, P. A. Keifer, F. Sun, L. H. Li, D. G. Martin, *J. Org. Chem.* **1990**, *55*, 4512; b) R. Sakai, K. L. Rinehart, Y. Guan, A. H.-J. Wang, *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 11456; total syntheses of **1**: c) E. J. Corey, D. Y. Gin, R. S. Kania, *J. Am. Chem. Soc.* **1996**, *118*, 9202; d) A. Endo, A. Yanagisawa, M. Abe, S. Tohma, T. Kan, T. Fukuyama, *J. Am. Chem. Soc.* **2002**, *124*, 6552; e) J. Chen, X. Chen, M. Bois-Choussy, J. Zhu, *J. Am. Chem. Soc.* **2006**, *128*, 87; semisynthesis of **1**: f) C. Cuevas, M. Pérez, M. J. Martín, J. L. Chicharro, C. Fernández-Rivas, M. Flores, A. Francesch, P. Gallego, M. Zarzuelo, F. de la Calle, J. García, C. Polanco, I. Rodríguez, I. Manzanares, *Org. Lett.* **2000**, *2*, 2545.
[3] For an example of base-induced epimerization at C3, see: J. W. Lane, Y. Chen, R. M. Williams, *J. Am. Chem. Soc.* **2005**, *127*, 12684.
[4] W. Jin, S. Metobo, R. M. Williams, *Org. Lett.* **2003**, *5*, 2095.
[5] a) B. Zhou, J. Guo, S. J. Danishefsky, *Org. Lett.* **2002**, *4*, 43; b) B. Zhou, S. Edmondson, J. Padron, S. J. Danishefsky, *Tetrahedron Lett.* **2000**, *41*, 2039; c) B. Zhou, J. Guo, S. J. Danishefsky, *Tetrahedron Lett.* **2000**, *41*, 2043.
[6] C. Chan, R. Heid, S. Zheng, J. Guo, B. Zhou, T. Furuuchi, S. J. Danishefsky, *J. Am. Chem. Soc.* **2005**, *127*, 4596.
[7] X. Chen, J. Chen, M. De Paolis, J. Zhu, *J. Org. Chem.* **2005**, *70*, 4397.
[8] For an excellent review of the tetrahydroisoquinoline alkaloids, see: J. D. Scott, R. M. Williams, *Chem. Rev.* **2002**, *102*, 1669.
[9] For a previous example of the connection of the subunits by amide bond formation to a secondary amine, see: E. J. Martinez, E. J. Corey, *Org. Lett.* **2000**, *2*, 993.
[10] A. K. Sinhababu, A. K. Ghosh, R. T. Borchardt, *J. Med. Chem.* **1985**, *28*, 1273.
[11] R. M. Williams, P. P. Ehrlich, W. Zhai, J. Hendrix, *J. Org. Chem.* **1987**, *52*, 2615.
[12] A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 2521.
[13] A. S. Thompson, G. R. Humphrey, A. M. DeMarco, D. J. Mathre, E. J. Grabowski, *J. Org. Chem.* **1993**, *58*, 5886.
[14] a) J. M. Bobbitt, J. C. Sih, *J. Org. Chem.* **1968**, *33*, 856; b) J. M. Bobbitt, T. E. Moore, *J. Org. Chem.* **1968**, *33*, 2958.
[15] K. Laali, R. J. Gerzina, C. M. Flajnik, C. M. Geric, A. M. Dombroski, *Helv. Chim. Acta* **1987**, *70*, 607.
[16] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1982**, *104*, 902.
[17] P. Four, F. Guibe, *Tetrahedron Lett.* **1982**, *23*, 1825.
[18] For a related example, see: M. J. Martin-Lopez, F. Bermejo-Gonzalez, *Tetrahedron Lett.* **1994**, *35*, 8843.
[19] E. J. Corey, J. Das, *Tetrahedron Lett.* **1982**, *23*, 4217.
[20] J. D. Hobson, J. G. McCluskey, *J. Chem. Soc.* **1967**, 2015.
[21] Direct McCluskey reaction of a MOM derivative of the type **9** failed owing to undesired reactivity at the MOM ether protecting group.
[22] For a related rearrangement versus selective reduction of an enamide epoxide, see: L. A. Mitscher, H. Gill, J. A. Filppi, R. L. Wolgemuth, *J. Med. Chem.* **1986**, *29*, 1277.

 © 2006 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

[23] S. Kim, K. H. Ahn, *J. Org. Chem.* **1984**, *49*, 1717.
[24] The use of $LiAlH_2(OEt)_2$, $LiAlH_3(OEt)$, and Red-Al gave intractable reaction products. Along these lines, $LiAlH(OtBu)_3$ reduced lactam **29** to oxazolidine **30**, however, in low conversion (10%), whereas boranes afforded the corresponding amine by exhaustive reduction of the lactam.

 © 2006 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim