Natural Products Synthesis

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Asymmetric Total Syntheses of Ecteinascidin 597 and Ecteinascidin 583**

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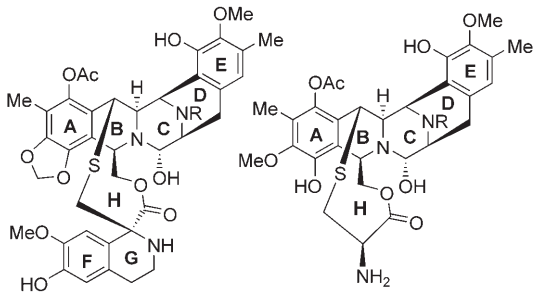
Dedicated to Professor Yulin Li on the occasion of his retirement

The ecteinascidins, a family of tetrahydroisoquinoline alkaloids isolated from the Caribbean tunicate *Ecteinascidia turbinata*,[1] display a wide range of antitumor and antimicrobial activities.[2] One member of this family, ecteinascidin 743 (Et 743, **1**; Scheme 1), is currently in late phase II/III clinical trials against ovarian, endometrium, and breast cancer, and several other types of sarcoma. The restricted natural availability of the ecteinascidins (1 g of Et 743 from 1 ton of tunicate) in conjunction with their potent antiproliferative activities and complex molecular architecture has made them attractive synthetic targets.[3] Since the landmark synthesis of Et 743 by Corey and co-workers in 1996,[4] Fukuyama and co-workers[5] and our research group[6] have also completed total syntheses of this molecule, and Danishefsky and co-workers[7] very recently reported a formal total synthesis of Et 743. A semisynthesis of Et 743 from cyanosafracin B was developed by Cuevas, Manzanares, and co-workers at PharmaMar,[8] and further synthetic approaches have been reported by a number of research groups.[9–14]



1 R = Me, Et 743
2 R = H, Et 729

3 R = Me, Et 597
4 R = H, Et 583

Scheme 1. Structure of representative ecteinascidins.

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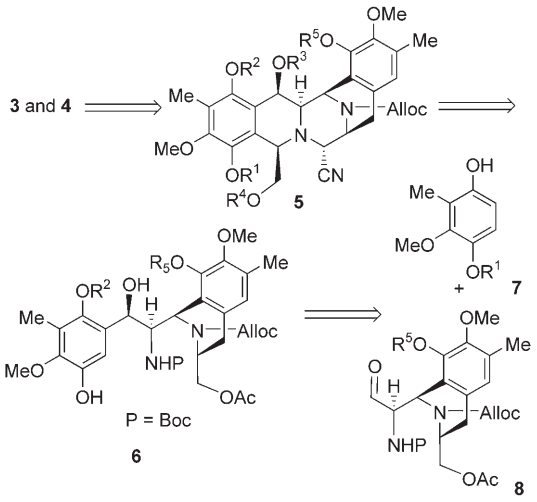
Supporting information for this article (experimental procedures, product characterization, and copies of ^{1}H and ^{13}C NMR spectra of synthetic Et 597 (**3**) and Et 583 (**4**)) is available on the WWW under http://www.angewandte.org or from the author.

Ecteinascidins 597 (Et 597, **3**) and 583 (Et 583, **4**; Scheme 1) are putative biosynthetic precursors of other ecteinascidins.[1d,15] Although the cytotoxicity of Et 597 (**3**), which lacks the third tetrahydroisoquinoline unit, is generally 2.5–10 times less potent than that of Et 743 against P 388, A 549, HT 29, and CV-1 cell lines, its antiproliferative activity is even greater than that of taxol and camptothecin.[1d] In continuation of our research towards the development of an efficient synthetic route to this family of marine natural products and on the structure–activity relationships (SARs) of these compounds, we became interested in the synthesis of Et 597 (**3**) and Et 583 (**4**). In a different approach to our previous strategy,[6] we envisaged that we could take advantage of the presence of two free hydroxy groups in ring A of **3** and **4**, as illustrated in Scheme 2. We planned to construct the

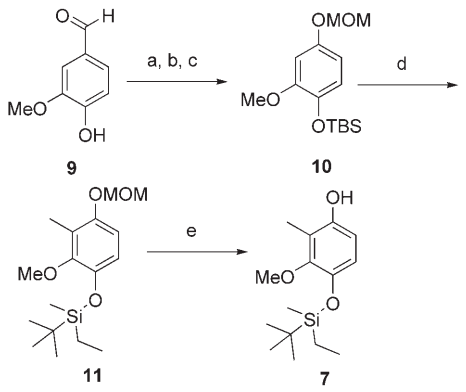


Scheme 2. Retrosynthetic analysis of Et 597 (**3**) and Et 583 (**4**). Alloc = allyloxycarbonyl, Boc = *tert*-butoxycarbonyl.

highly oxygenated A–B ring system by starting from phenol **7** and tetrahydroisoqinoline **8** and carrying out a sequence of phenolic aldol condensations followed by a Pictet–Spengler reaction. An intramolecular Strecker reaction would then afford the entire A–B–C–D–E pentacycle, whereupon the closure of the 10-membered lactone by formation of the carbon–sulfur bond would lead to the natural products.

The synthesis of the aromatic segment **7** is summarized in Scheme 3. 3-Methoxy-4-hydroxybenzaldehyde (**9**) was converted into **10** through a well-established three-step sequence. Interestingly, *ortho* lithiation of **10** followed by the addition of methyl iodide[16] gave a compound in which both the aromatic ring and the TBS protecting group had been methylated. Under optimized conditions (3 equivalents of *n*BuLi, 4 equivalents of MeI), the dual-methylation product **11** was isolated in 92 % yield. The MOM group could be removed without touching the silyl ether by treatment with TMSBr to provide phenol **7** in excellent yield.[17]

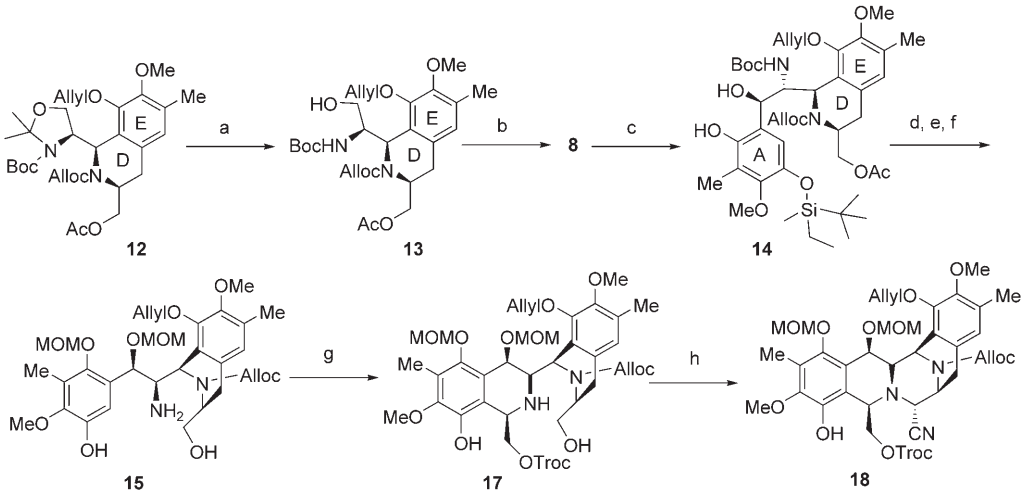
Our synthetic route to the pentacyclic compound **18** is depicted in Scheme 4. The synthesis of the tetrahydroisoquinoline **12** featured a highly diastereoselective Pictet–Spengler condensation of the (*S*)-Garner aldehyde with (*S*)-3-hydroxy-4-methoxy-5-methylphenylalanol.[6,18] The selective



Scheme 3. Synthesis of the A-ring unit **7**: a) TBSCl, imidazole, DMF, RT, 98 %; b) mCPBA, $CHCl_3$, 45 °C; then Na_2CO_3, MeOH, RT, 85 %; c) MOMCl, DIPEA, CH_2Cl_2, 0 °C → reflux, 96 %; d) *n*BuLi, THF, −10 °C; then MeI, −78 °C → RT, 92 %; e) TMSBr, CH_2Cl_2, −20 → 0 °C, 90 %. TBS = *tert*-butyldimethylsilyl, mCPBA = *m*-chloroperbenzoic acid, MOM = methoxymethyl, DIPEA = *N*,*N*-diisopropylethylamine, DMF = *N*,*N*-dimethylformamide.

hydrolysis of the oxazolidine moiety in **12** was more difficult than expected. Eventually, reaction conditions that were previously developed for the cleavage of acetonides ($CeCl_3 \cdot 7H_2O$, oxalic acid, acetonitrile, room temperature) afforded alcohol **13** in 91 % yield.[19] Swern oxidation[20] of the primary alcohol furnished the corresponding aminoaldehyde **8**, which without purification underwent the stereoselective phenolic aldol condensation with the magnesium phenolate of **7**[21,22] to provide the *syn* aminoalcohol **14** in 74 % yield. The *anti* aminoalcohol was neither isolated nor detected. The existence of rotamers made NMR spectroscopic analysis of **14** difficult, and it was hard to determine if this product was a mixture of two diastereomers with respect to the stereogenic silicon center.[23] Nevertheless, the question of diastereomers was of no consequence, as the silyl protecting group was due to be removed in the next step. Compound **14** was transformed into aminoalcohol **15** in excellent overall yield by a three-step sequence: 1) protection of the phenol and secondary alcohol as the corresponding methoxymethyl ethers, 2) simultaneous removal of the *N*-Boc and *O*-silyl protecting groups according to the procedure of Sakaitani and Ohfune,[24] and 3) hydrolysis of the acetate. The Pictet–Spengler reaction[25] of **15** and $TrocOCH_2CHO$ (**16**; prepared in two steps from ethyleneglycol)[26] was the key step of our synthesis. To our pleasure, the desired transformation proceeded efficiently in dichloromethane in the presence of acetic acid and 3-Å molecular sieves to provide **17** as a single diastereomer in 90 % yield. Swern oxidation of the aminoalcohol **17** followed by a zinc chloride catalyzed intramolecular Strecker reaction provided aminonitrile **18** as a single stereoisomer to complete the highly efficient construction of the pentacyclic ring system.

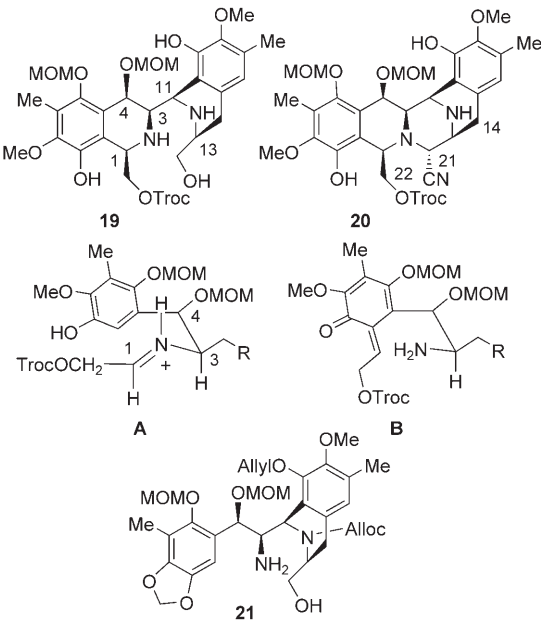
The relative configuration of compound **17** was determined upon its conversion into **19**. The characteristic NOEs observed between H1/H3, H3/H4, and H11/H13 (ecteinascidin numbering) indicated that the configuration of **19**, and hence that of **17**, is 1*R*, 3*R*, 4*R*, 11*R*, 13*S*. The configuration at C21 was determined to be *R* by detailed NMR spectroscopic



Scheme 4. Synthesis of the pentacyclic compound **18**: a) $CeCl_3 \cdot 7H_2O$, oxalic acid, acetonitrile, RT, 91%; b) oxalyl chloride, DMSO, CH_2Cl_2, −60°C, then Et_3N; c) MeMgCl, THF, **7**; then **8**, CH_2Cl_2, RT, 74%; d) MOMCl, DIPEA, $CHCl_3$, 0°C→reflux, 88%; e) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78°C→RT; then KF, MeOH, RT, 86%; f) K_2CO_3, MeOH, RT, 94%; g) AcOH, $TrocOCH_2CHO$ (**16**), 3-Å MS, CH_2Cl_2, RT, 90%; h) oxalyl chloride, DMSO, CH_2Cl_2, −60°C; then TMSCN, $ZnCl_2$, CH_2Cl_2, RT, 87%. DMSO = dimethyl sulfoxide, Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl, Troc = 2,2,2-trichloroethoxycarbonyl.

studies of the *N*-de-Alloc derivative **20** (NOEs observed for H21/H22 and H14/H21; Scheme 5).

The high diastereoselectivity observed in the condensation of **15** and **16** could be explained by assuming that the iminium intermediate had a *trans* configuration and that the substituents at C3 and C4 were both pseudoequatorial (**A**, Scheme 5).[27] However, at the present stage an alternative sequence involving a phenolic aldol condensation and β elimination to give the orthoquinone methide intermediate **B** (Scheme 5) followed by intramolecular Michael addition of the tethered amine can not be eliminated as a possibility.[28] It is nevertheless interesting to note that the presence of the free

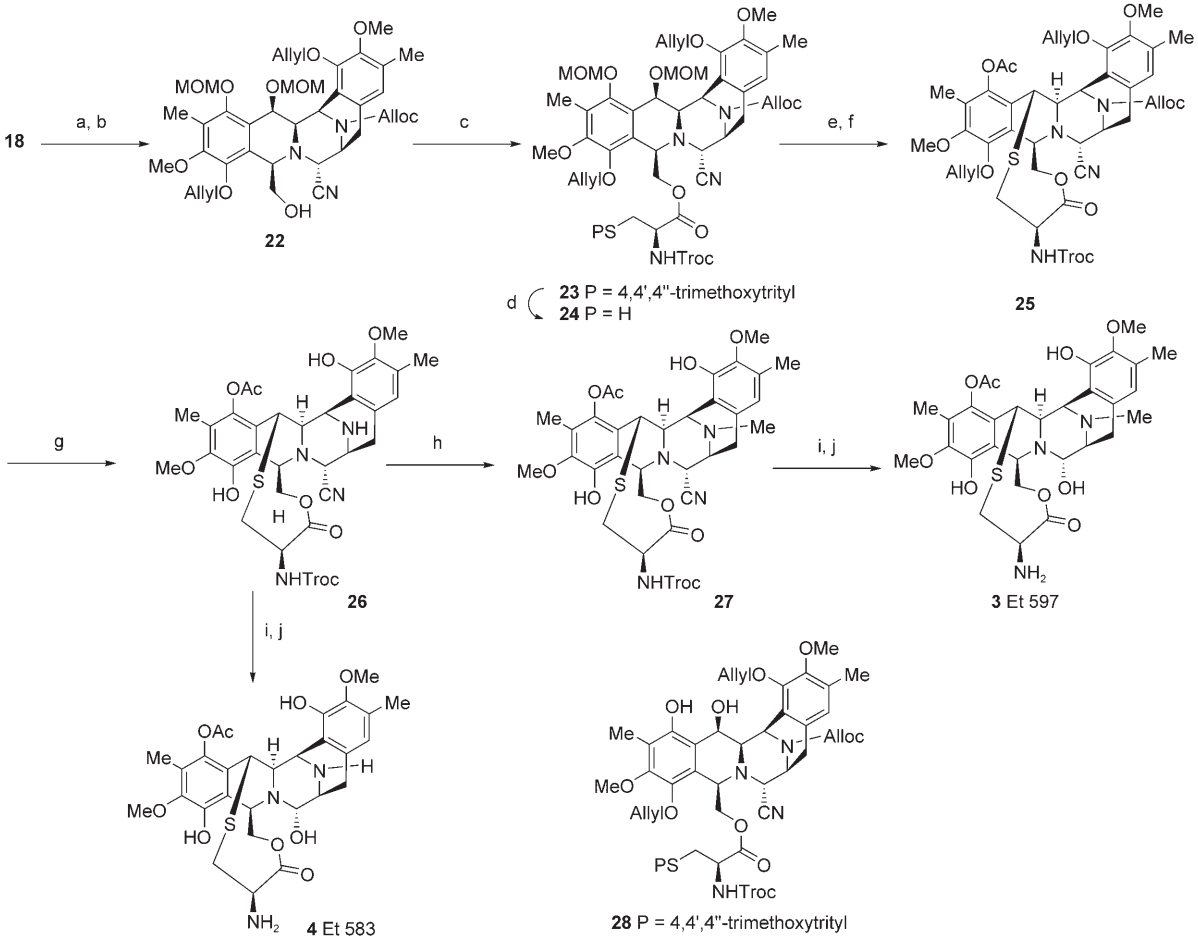


Scheme 5. Structures for the discussion of configuration and possible reaction pathways.

phenol group in ring A is essential to the success of the reaction; the condensation of amine **21** with 2-benzyloxyacetaldehyde (or ethyl glyoxylate) failed to provide the desired tetrahydroisoquinoline.

The total synthesis of Et 597 (**3**) and Et 583 (**4**) was completed as shown in Scheme 6. Unmasking of the Troc-protected primary alcohol under reductive conditions followed by chemoselective allylation of the phenol group provided compound **22**, which was coupled with (*R*)-*N*-Troc-*S*-4,4′,4″-trimethoxytritylcysteine to afford the corresponding ester **23** in excellent yield. The cyclization of **23** was examined under a variety of reaction conditions; the acid (*p*-toluenesulfonic acid, TFA, $MeSO_3H$, TMSBr), the solvent (CH_2Cl_2, toluene, 2,2,2-trifluoroethanol, MeCN), and the temperature were varied, and the reaction was carried out in the presence or absence of molecular sieves. Unfortunately, no combination provided the desired 10-membered lactone **25**. The attempted cyclization of phenol **28** also met with failure. We then decided to separate the S-deprotection and cyclization steps. Removal of the *S*-4,4′,4″-trimethoxytrityl group from **23** with Et_3SiH/TFA afforded the stable thiol **24** in 88% yield after flash column chromatography.[29] Gratifyingly, the treatment of thiol **24** with TMSBr afforded the bridged macrocycle **25**, after the phenol had been masked as the corresponding acetate, in 60% yield.[30] In this simple experiment, a complex reaction sequence involving *O*-MOM deprotection, 1,4-elimination to give the orthoquinone methide,[31] and macrocyclization through an intramolecular Michael addition occurred in a highly ordered manner to bring about the key C–S bond formation.

Simultaneous removal of the *N*-Alloc and *O*-allyl functionalities as described by Guibé and co-workers[32] provided amine **26** in 85% yield. A sequence of reductive N methylation, removal of the *N*-Troc group (zinc/AcOH), and conversion of the aminonitrile functionality into a hemiaminal ($AgNO_3$ in a mixture of acetonitrile and water) afforded



Scheme 6. Synthesis of Et 597 (**3**) and Et 583 (**4**): a) Zn, AcOH, Et_2O, RT, 90%; b) allyl bromide, K_2CO_3, acetonitrile, RT, 94%; c) EDCI, DMAP, (*R*)-*N*-Troc-*S*-4,4′,4″-trimethoxytritylcysteine, CH_2Cl_2, RT, 93%; d) Et_3SiH, TFA, CH_2Cl_2, RT, 87%; e) TMSBr, CH_2Cl_2, −20°C→10°C; f) Ac_2O, pyridine, DMAP, CH_2Cl_2, RT, 60%; g) $[Pd(PPh_3)_4]$, nBu_3SnH, AcOH, CH_2Cl_2, RT, 85%; h) CH_2O, $NaBH_3CN$, AcOH, MeCN/MeOH, RT, 95%; i) Zn, AcOH, Et_2O, RT, 89% for Et 597, 86% for Et 583; j) $AgNO_3$, MeCN/H_2O, RT, 92% for **3**, 88% for **4**. DMAP = 4-dimethylaminopyridine, TFA = trifluoroacetic acid, EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride.

ecteinascidin 597 (**3**) in excellent overall yield. Similarly, amine **26** was converted into ecteinascidin 583 (**4**) in a two-step sequence. Synthetic Et 597 (**3**) and Et 583 (**4**) exhibited physical, spectroscopic, and spectrometric characteristics (^1H, ^{13}C NMR, IR, $[\alpha]_D$, and HRMS) identical to those reported for the natural products.

In summary, convergent total syntheses of Et 597 (**3**) and Et 583 (**4**) have been completed for the first time from readily accessible starting materials. Notable features of our approach include: 1) a stereoselective aldol reaction for the coupling of the A-ring moiety **7** with the D–E unit **8**, 2) a highly stereoselective Pictet–Spengler reaction for the construction of the B ring, and 3) TMSBr-promoted macrocyclization of the thiol **24** to give the 1,4-bridged 10-membered ring. This straightforward synthesis does not require sophisticated reaction conditions and should potentially be amenable to large-scale production. We are currently exploiting this strategy for the synthesis of ecteinascidin analogues for detailed SAR studies.[33]

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[26] $TrocOCH_2CHO$ (**16**) was prepared in two steps from ethyleneglycol: 1) TrocCl (1 equiv), pyridine (1.1 equiv), ethyleneglycol (10 equiv), CH_2Cl_2, 86 %; 2) Dess–Martin periodinane (1.1 equiv), CH_2Cl_2, 80 %. Compound **16** has a high tendency to undergo trimerization and should be used immediately after preparation.

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[33] Owing to the restricted availability of this family of natural products, there are very few reports in the literature that deal with SARs of these compounds, despite their medical importance; see: E. J. Martinez, T. Owa, S. L. Schreiber, E. J. Corey, *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 3496 – 3501.

