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Synthetic explorations in the saframycin-ecteinascidin series: construction of major chiral subunits through catalytic asymmetric induction

Bishan Zhou,[a] Scott Edmondson,[a] Juan Padron [a] and Samuel J. Danishefsky [a,b,*]

[a]*The Department of Chemistry, Columbia University, Havemeyer Hall, New York, NY 10027, USA*
[b]*The Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Ave., New York, NY 10024, USA*

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Abstract

The major subunits needed to reach the titled targets have been assembled by chemistry, which included *p*-Claisen rearrangement, asymmetric epoxidation and asymmetric dihydroxylation.

The screening of natural product sources for new drug candidates with useful therapeutic margins has led to a variety of novel structures. One of the most fascinating and promising of these is ecteinascidin 743 (**1**=ET 743) derived from the marine tunicate *Ecteinascidia turbinata*.[1] The novel structure of ET 743, its difficult availability, and its exceedingly potent cytotoxicity (as well as its advancement to clinical trials) conspire to render it an attractive target for total synthesis. This goal was undertaken and accomplished in a most interesting fashion by Corey and co-workers.[2] Follow-up studies by Corey, Schreiber[3] and co-workers resulted in the demonstration that a significantly simplified version of **1** (ie: phthalascidin) retains the cytotoxicity of the natural product.

Our interest in ET 743 was much influenced by the considerations described above, with an additional caveat. Some years ago, well before the ecteinascidins were known, we had accomplished what was then the only total synthesis of quinocarcinol.[4] We wondered whether the central Mannich-like envelopment strategy, which was our take home lesson in the quinocarcin series, could be adapted to the ET problem. This matter will be considered in greater detail in the subsequent letter.[5]

We undertook to test these and other relevant questions in the context of a synthesis directed to systems of the type **3**. From the perspective of its two aromatic sectors, **3** can be viewed as more closely related to the saframycin series (**2**) than to ET.[6] Indeed, the aromatic rings in **3** can be regarded as modified hydroquinone versions of the quinone moieties of saframycin, with the important proviso that **3** also

* Corresponding author.

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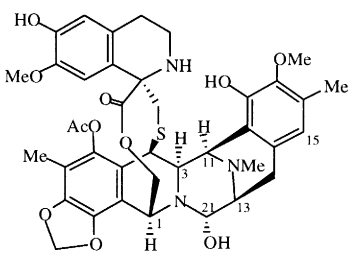
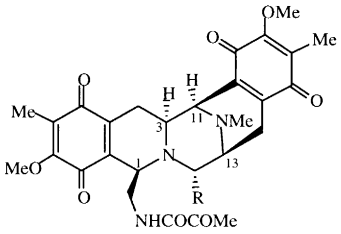
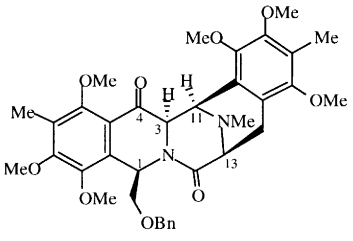
contains a 4-oxo group. This function, in the context of appropriate aromatic domains, is potentially valuable for synthesizing ET and a new range of analogs thereof.



1 ET 743

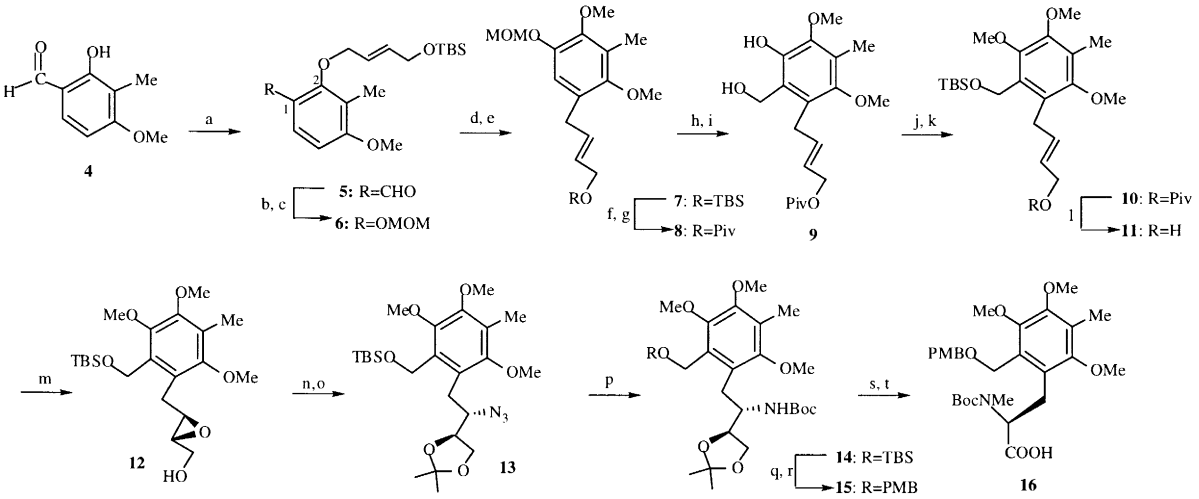


2 Saframycin B (R = H)
Saframycin A (R = CN)
Saframycin S (R = OH)



3 4-Oxy-saframycin

Our approach to **3** contemplated the merger of two moieties, **16** and **25**, wherein each component would bear the absolute configuration appropriate to the goal system in high enantiomeric excess. In this disclosure, we describe the pathways, which we followed for reaching the key building blocks. Our inquiry was directed to the applicability of catalytic oxidative asymmetric induction to these targets, and was strongly influenced by precedents from Sharpless.[7a–c]



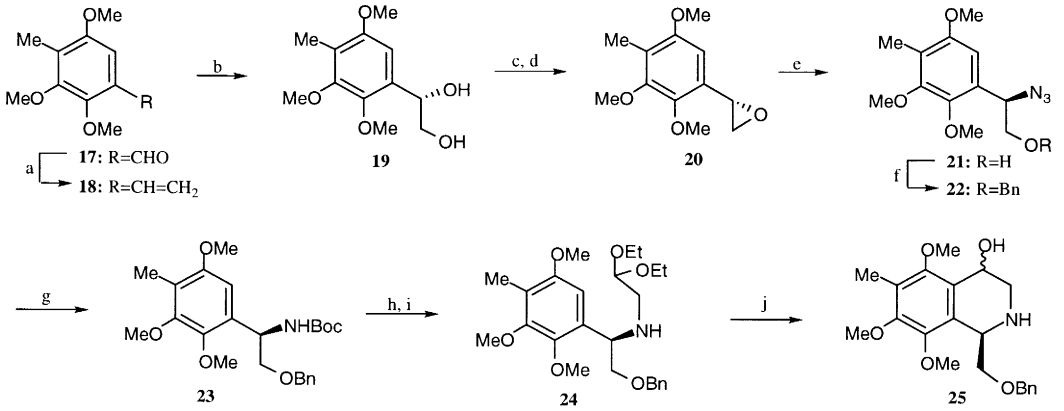
Scheme 1. (a) 1.1 equiv. $BrCH_2CH{=}CHCH_2OTBS$, 1.5 equiv. K_2CO_3, CH_3CN, reflux, 5 h, 100%; (b) 1.1 equiv. 30%, H_2O_2, cat. SeO_2, *t*-BuOH, 40°C, 5 h, then Et_3N, MeOH, 85%; (c) 1.1 equiv. MOMCl, 1.5 equiv. $(i\text{-Pr})_2NEt$, CH_2Cl_2, 80°C, 12 h, 100%; (d) 1.1 equiv. Me_2NPh, toluene, 210°C, 12 h, 96%; (e) MeI(xs), 1.5 equiv. K_2CO_3, CH_3CN, reflux, 12 h, 87%; (f) 1.5 equiv. TBAF, THF, 1 h; (g) 1.1 equiv. PivCl, pyridine:CH_2Cl_2 (1:20), 3 h; (h) 3N HCl, THF–*i*-PrOH (2:1), 12 h, 99% for three steps; (i) 3 equiv. Et_2AlCl, $(CH_2O)_n$(xs), CH_2Cl_2, 12 h, 96%; (j) MeI(xs), 1.5 equiv. K_2CO_3, $CHCl_3$:MeOH (2:1), reflux, 12 h, 90%; (k) 1.2 equiv. TBSCl, 1.5 equiv. imidazole, cat. DMAP, CH_2Cl_2, 1 h, 99%; (l) 2.5 equiv. DIBAL-H, CH_2Cl_2, −78°C, 30 min, 94%; (m) 8% (D)-DET, 5.6% $Ti(OiPr)_4$, 2 equiv. *t*-BuOOH, m.s. 4 Å, −20°C, 1 day, 98% (95% ee); (n) 3.5 equiv. $Ti(OiPr)_2(N_3)_2$, PhH, 80°C, 76% (single isomer); (o) $(MeO)_2CMe_2$:acetone (1:2), cat. *p*-TsOH·H_2O, 10 min, 100%; (p) H_2, Pd/C, EtOAc, 1.2 equiv. $(Boc)_2O$, 5 h, 100%; (q) 1.5 equiv. TBAF, THF, 1 h; (r) 1.2 equiv. PMBCl, 2 equiv. NaH, cat. *n*-BuN^+I^-, THF:DMF (5:1), 5 h, 96% for two steps; (s) MeI(xs), 5 equiv. NaH, THF:DMF (5:1), 12 h, reflux, 93%; (t) (i) 80% AcOH, 12 h; (ii) 0.2 equiv. $KMnO_4$, 4 equiv. $NaIO_4$, 0.5 equiv. Na_2CO_3, dioxane:H_2O (2.5:1), 10 h, 95%

We begin with the route followed to reach **16** (Scheme 1). The starting material was the readily accessible **4**,[8] obtained from the commercially available 2,4-dimethoxy-3-methyl benzaldehyde. Compound **4** was converted by *O*-alkylation, as shown to ether **5**. Dakin-like[9] oxidative cleavage of the aryl aldehyde linkage generated a formate, which was deacylated by *trans* esterification. Protection of the resultant

phenol afforded **6**. It will be recognized that the allylic ether had served to protect the C2 hydroxyl group while the substituent at C1 was being adjusted in a constructive way. At this point, *p*-Claisen rearrangement and sequential protection of the phenol and primary allylic alcohol functions, as indicated, led to **7** and thence **8**. Cleavage of the MOM group was now readily accomplished and the resultant phenol function was exploited to bring about *O*-hydroxymethylation (see compound **9**). Selective methylation of the phenolic hydroxyl and silylation of the primary benzylic alcohol led to **10**.

The setting was in place to introduce the L-amino acid functionality. An allylic alcohol (see structure **11**) was exposed on cleavage of the pivaloate. Sharpless K. B.,[7a] under the conditions shown, led to **12** in high ee (>95%). Azidolysis of the oxirane linkage under titanium mediated direction[7c] afforded a diol. To allow for building the required *N*-methyl ^{t}Boc linkage, the diol was protected as its acetonide (see structure **13**). From that point, the azide linkage was reductively cleaved in the presence of Boc anhydride to afford **14**. Subsequent to cleavage of the TBS group and installation of a *p*-methoxybenzyl function, **15** was in hand. Following *N*-methylation, hydrolysis of the acetonide, and oxidative cleavage of the diol,[10] compound **16** was secured.

The synthesis of **25**, with the suitable *S* configuration at the future C13, commenced with the known and readily available benzaldehdye **17**,[11] which was converted to **18** (Scheme 2). Asymmetric dihydroxylation[7b] of the styrene like double bond through the action of AD mix-α gave rise to **19** (>95% ee), from which the epoxide **20** was derived as shown. Azidolysis of the epoxide compound, under the conditions indicated, resulted in a 6.5:1 preference for attack at the benzylic, as opposed to primary carbon. The major product, **21**, was converted to its *O*-benzyl derivative **22**.



Scheme 2. (a) 1.6 equiv. $Ph_3P{=}CH_2Li$, THF, 0°C, 1 h, 96%; (b) 1.1 equiv. AD-mix-α, *t*-BuOH:H_2O (1:1), 0°C, 3 d, 99%; (c) 1.1 equiv. TsCl, pyridine:CH_2Cl_2 (1:1), 1 d, 95%; (d) 2 equiv. K_2CO_3, MeOH, 4 h, 95%; (e) 4 equiv. NaN_3, 15 equiv. $LiClO_4$, CH_3CN, 60°C, 5 h, (2°:1°=6.5:1); (f) 1.1 equiv. BnBr, 5 equiv. NaH, cat. *n*-BuN^+I^-, THF, 5 h, 90% for 2 steps; (g) H_2, Pd/C, EtOAc, 1.2 equiv. $(Boc)_2O$, 5 h, 100% (h) TFA:CH_2Cl_2 (1:2), then $NaHCO_3$ (i) 4 equiv. K_2CO_3, 5 equiv. $BrCH_2CH(OEt)_2$, CH_3CN, reflux, 3 d, 80% for 2 steps; (j) 12N HCl:THF (1:1), then NaOH, 88% (β-OH:α-OH=4:1)

The azide linkage was reduced in the presence of Boc anhydride to afford **23**. The ^{t}Boc protection maneuver was conducted for convenience in the isolation process. Cleavage of the Boc group of **23** was followed by monoalkylation of the resultant amine function with diethylbromoacetal in high yield (see compound **24**). Finally, the tetrahydroisoquinole ring was produced by the Pomerantz–Fritsch type cyclization of **24**.[12] Product **25** was obtained as a 4:1 mixture of β,α stereoisomers at the future C4. As will be seen,[5] this stereochemical issue is without consequence, since this center is destined to become a ketone in short order.

In summary, we have shown that a suitably directed *p*-Claisen rearrangement followed by Sharpless K. B.[7a] can be used to generate a significantly functionalized tyrosine (see compound **16**) analog. Furthermore, Sharpless K. B.[7b] followed in due course by a modified Pomerantz–Fritsch cyclization, has been used to reach a valuable heavily functionalized tetrahydroisoquinoline subtype **25** in high ee.

Acknowledgements

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