

Studies Directed to the Total Synthesis of ET 743 and Analogues Thereof: An Expeditious Route to the ABFGH Subunit

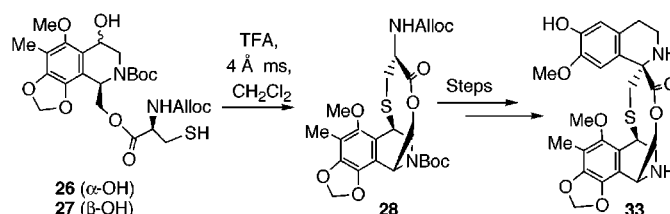
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ABSTRACT



In model studies directed to the total synthesis of Et743, a strategic S–C bond formation in systems **26** and **27** was demonstrated. It was further shown that Pictet–Spengler cyclization leading to spiro product **33** exhibits very high stereoselection.

Ecteinascidin 743¹ (Et743), **1**, is one of several related marine alkaloids isolated from the Caribbean tunicate *Ecteinascidia turbinata*. Although extracts from this organism have been studied since the 1960s, the isolation of pure substances did not occur until 1986. In terms of its presentation of the core pentacyclic A–E ring system, Et743 bears significant structural homology to the saframycin family of antibiotics as well as to related compounds.² The largest difference is that in Et743, position 4 is at a higher oxidation level than

it is in the case of the saframycins. The additional functionality in **1** takes the form of a novel 10-membered ring. This sulfur-containing macrolactone is itself spiro linked to a tetrahydroisoquinoline.

Aside from its intriguing architecture, Et743 commands interest as a potential anticancer agent. It is exceedingly cytotoxic with in vitro IC₅₀ values in the 0.1–1 ng/mL range. On the basis of this extraordinary in vitro activity in several cell lines, the compound was advanced through in vivo animal models and is now in human clinical trials.³

The drug availability issue in terms of isolation from natural sources is quite serious. Corey and Gin described the first and thus far only total synthesis of Et743.⁴ This accomplishment, which required the solution of a host of

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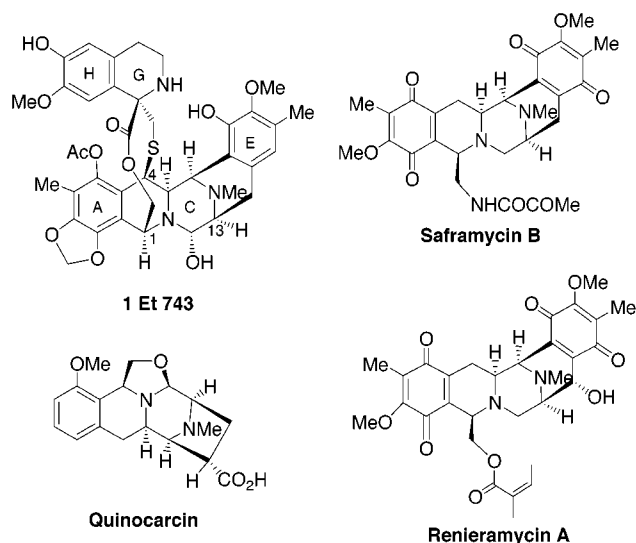
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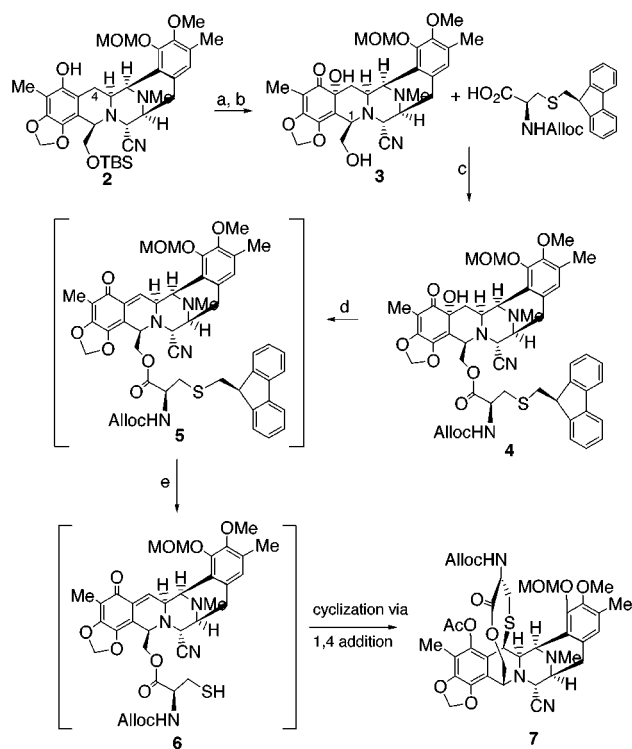
very complicated problems, provided the material for early clinical evaluations. Subsequently, access to Et743 has been eased by partial synthesis of the drug from cyanosafracin B, benefiting extensively from the findings of the late stages of the Corey–Gin total synthesis.⁵



In both the Corey–Gin total synthesis and the Pharma Mar partial synthesis, a bis hydroquinone version of a saframycin lacking any functionality at C4 serves as a precursor for angular oxidation (cf. **2** → **3**). Coupling of a free hydroxymethyl group from C1 to a suitable cysteine derivative gives rise to **4**. In a most elegant maneuver, the cysteine thiol adds to a fugitive orthoquinone methide, generated upon activation of the α -ketol moiety (cf. **5** → **6** → **7**, Scheme 1).

In the research described herein, we hoped to evaluate a different approach to closing the 10-membered sulfur-containing lactone. It is in the nature of our approach to the saframycins that the pentacyclic ring system is synthesized with potentially valuable functionality in place at C4. Our systems are established from an intramolecular Mannich-like reaction wherein the formyl group of a benzaldehyde residue is sequestered between an *N*-methylamino group and an enol (see **8** → **9**).⁶ The question we asked is whether one could close such a 10-membered lactone by displacement of a C4 leaving group, derived from the C4 ketone that flows from our synthesis (cf. **10** → **11**). In this paper, we demonstrate, in a model system, that such a cyclization is indeed feasible and that it takes place independently of the relative configurations at C1 and C4. We also report on the

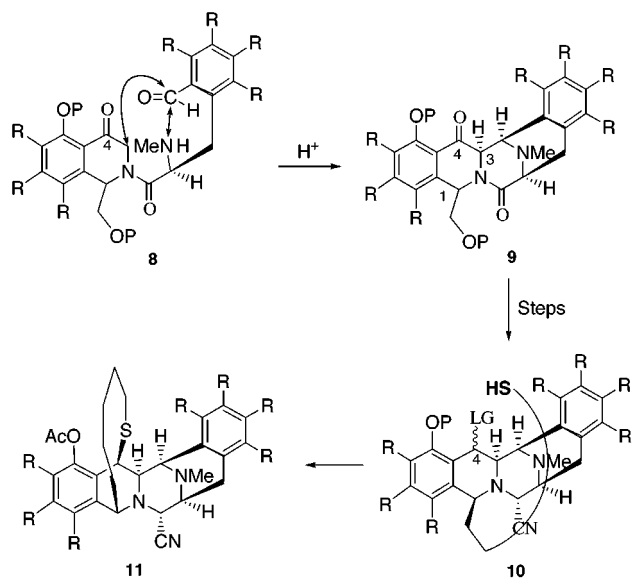
Scheme 1. Corey–Gin Synthesis of ET743 (Late Stages)^a



^a Reagents and conditions: (a) (PhSeO)₂O, CH₂Cl₂; (b) TBAF, THF; (c) EDC, DMAP, CH₂Cl₂; (d) (i) Tf₂O, DMSO, –40 °C; (ii) (*i*-Pr)₂NEt, 0 °C; (iii) *t*-BuOH, 0 °C; (e) (i) *N*-*t*-Bu-*N*',*N*',*N*'',*N*'''-tetramethylguanidine, 0 °C, (ii) Ac₂O.

surprising stereoselectivity in fashioning the C1' spiro linkage via a Pictet–Spengler reaction on a simple model that lacks the massive steric bias of the previously studied substrate in the Corey–Gin total synthesis (Scheme 6).

Scheme 2

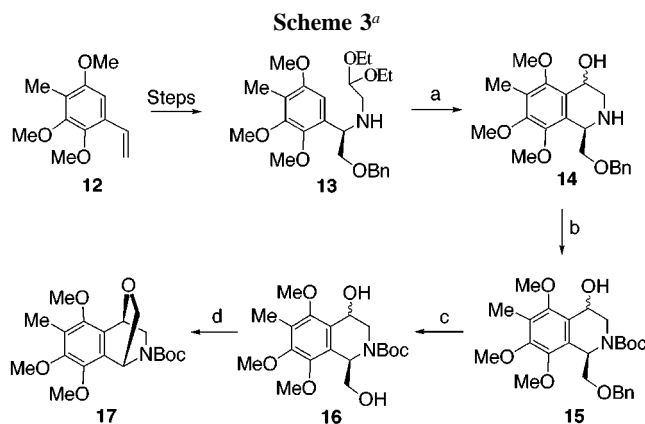


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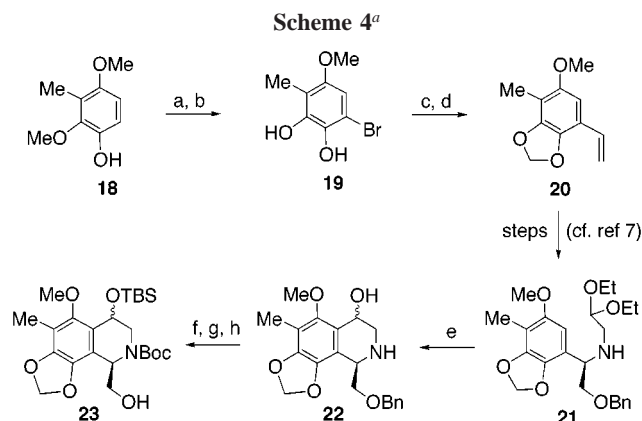
(6) Zhou, B.; Guo J.; Danishefsky, S. J. *Tetrahedron Lett.* **2000**, *41*, 2043. Since this work appeared, we now recognize that in this cyclization, the stereochemistry at C1 controls the sense of the Mannich closure at C3. The reaction is such that the hydrogens at C1 and C3 will emerge trans. The origin of this effect, and its consequences for reaching Et743 by chemical synthesis has been discussed extensively in ref 10 and will be described shortly.

Earlier, we had reported on the use of the Pomeranz–Fritsch reaction to gain access to optically pure tetrahydroisoquinoline substrates.⁷ The enantiomeric definition at C1 arose from Sharpless asymmetric dihydroxylation⁸ of the starting styrene **12** en route to optically defined amine **13**. Cleavage of the acetal set into motion the cyclization reaction that led to **14**. In this product, C1 is enantiomerically homogeneous, but C4 emerges as a mixture of diastereomers. After the NH function was protected as a urethane (see **15**), cleavage of the primary ether function afforded **16** in 99% yield. Our first encouraging finding was that treatment of this mixture with TFA in the presence of molecular sieves provided **17**. We construed this cyclization to a six-membered ring as an encouraging precedent for the more ambitious case we had in mind (cf. **10** → **11**, Scheme 2).



^a Reagents and conditions: (a) 6N HCl, THF, H₂O, 80%; (b) Boc₂O, Et₃N, EtOAc, >90%; (c) H₂ (1 atm), 10% Pd/C, EtOAc, 99%; (d) TFA, 4 Å mol sieves, CH₂Cl₂, 80%.

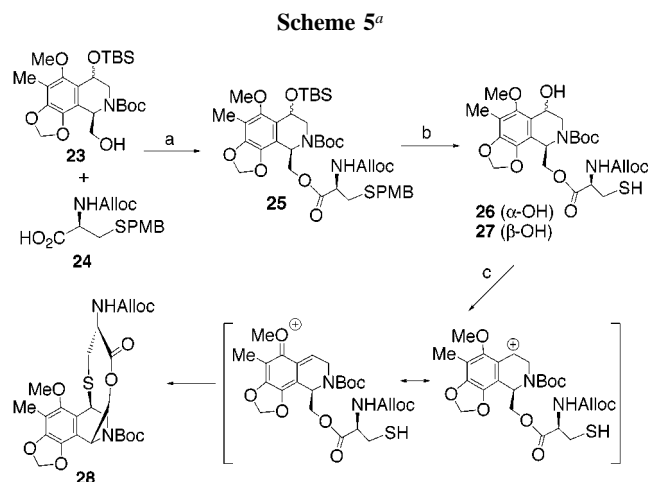
For this purpose, we turned to the Et743 related ring A tetrahydroisoquinoline **22**, which was smoothly synthesized



^a Reagents and conditions: (a) Br₂, K₂CO₃, CH₂Cl₂, –78 °C, 80%; (b) AlCl₃, CH₂Cl₂, 99%; (c) BrCH₂Cl, Cs₂CO₃, MeCN, reflux, 82%; (d) vinyltributyltin, Pd(PPh₃)₄, toluene, reflux, 90%; (e) 6 N HCl, dioxane, H₂O, 86%; (f) Boc₂O, Et₃N, EtOAc, >90%; (g) TBSCl, DMAP, imidazole, CH₂Cl₂, 81%; (h) H₂ (1 atm), 10% Pd/C, EtOAc, 99%.

as shown (Scheme 4). The route started from phenol **18**, known from earlier work in our laboratory on an unrelated problem.⁹ It continued through bromocatechol **19** and thence to styrene **20**, which was advanced as above to amine **21** and thence to diastereomer mixture **22**. Following protection of the NH group as a Boc derivative and silylation of the secondary hydroxyl group, the primary ether was debenzylated as shown (see intermediates **23**).

Following precedents of the Corey–Gin synthesis, the alcohols **23** were coupled to freshly prepared cysteine acid **24**.^{4,10} The desired esters **25** were produced in excellent yield (see Scheme 5). Subsequent deprotection of the PMB group



^a Reagents and conditions: (a) EDC, DMAP, CH₂Cl₂, 95%; (b) Hg(O₂CCF₃)₂, 80% AcOH, 80%; (c) TFA, 4 Å molecular sieves, CH₂Cl₂, 95%.

occurred smoothly to afford **26** and **27**. These two easily separable, potential cyclization substrates were advanced individually for the purpose of gaining insight into the role of C4 stereochemistry on the possibilities of cyclization. In the event, **26** and **27** were each treated with TFA in dry CH₂Cl₂ in the presence of activated 4 Å molecular sieves. Remarkably, in less than 5 min, each substrate produced the same product, **28**, in comparably high yields.

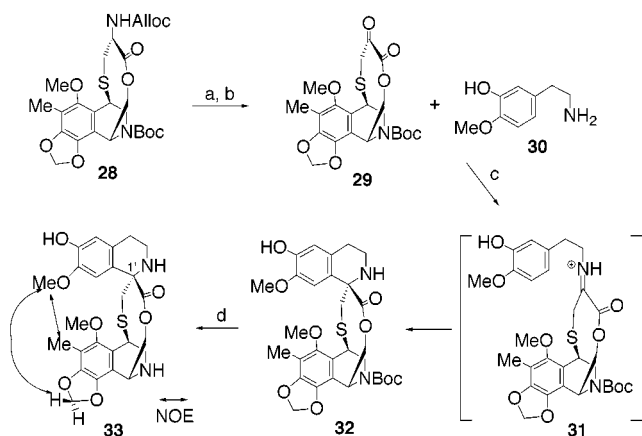
Our final subgoal was to reach compounds such as **32** and **33** where the C, D and E rings of ET743 have been deleted. We also hoped to explore the issue of stereoselectivity in the Pictet–Spengler reaction leading to **32** (vide infra). Toward these ends, the *N*-allyloxycarbonyl group of **28** was cleaved by treatment with Bu₃SnH and Pd(PPh₃)₂Cl₂ in the presence of excess of AcOH (Scheme 6). The resulting

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Scheme 6^a

^a Reagents and conditions: (a) Bu_3SnH , $\text{Pd}(\text{Ph}_3\text{P})_2\text{Cl}_2$, AcOH , 90%; (b) pyridine-4-carboxaldehyde methiodide, DBU, DMF, CH_2Cl_2 , 85%; (c) **30**, silica gel, dry EtOH, 80%; (d) TFA, CH_2Cl_2 , 89%.

α -amino lactone was oxidized to the corresponding α -keto lactone by transamination with the methiodide of pyridine-4-carboxaldehyde (see **29**). The reaction of ketone **29**, conducted with amine **30** as described by Corey and Gin in a more complex setting,⁴ generated the spiro tetrahydroisoquinoline **32** in an apparently stereospecific fashion. Due to the rotameric states of **32**, it was difficult to determine the orientation of the spiro attachment. The *N*-Boc linkage was accordingly cleaved by TFA treatment, affording the amine

33. NOE measurements on **33** established that the orientation at C-1' corresponded to that required for Et743. Whether this outcome is the result of thermodynamic control or reflects some long-range stereochemical preferences in mutual presentation of the aromatic sectors of the iminium intermediate (cf. **31**) at the kinetic level is not known. In this regard, it is tempting to propose that as the H ring attacks the iminium ion in **31**, the resultant transient electron-deficient cyclohexadienone moiety is stabilized by stacking to the electron-rich A ring. In this way, the observed sense of face selectivity would be rationalized.

In summary, we have demonstrated a sulfur–carbon bond formation in a unique and efficient way in both **26** and **27**. The route to these compounds takes advantage of our Mannich strategy (cf. **8** \rightarrow **9**) for generating valuable functionality at C4 in saframycins. Research directed to application of this chemistry to more advanced Et743 intermediates is in progress.

Acknowledgment. This work was supported by the National Institutes of Health (Grant Nos. CA-28824 and HL-25848 (S.J.D.)). B.Z. gratefully acknowledges the Pharmacia Corp. for a predoctoral fellowship. J.G. gratefully acknowledges the Pharma Mar Co. for a postdoctoral fellowship.

Supporting Information Available: Selected experimental procedures are provided (General Methods, compounds **12–14**, **17–23**, **25**, **28**, **29**, **32**, and **33**). This material is available free of charge via the Internet at <http://pubs.acs.org>. OL016844K