

## AN IMPROVED SYNTHESIS OF THE ABC RING MODEL OF ECTEINASCIDINS

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**Abstract**—An improved synthesis of 1,2,3,4,5,6-hexahydro-1,5-imino-9-methoxy-3,8,11-trimethyl-4-oxo-3-benzazocine (**6**) as an ABC ring model compound of ecteinascidins from 3-(4-methoxy-3-methylphenylmethyl)-1-methyl-2,5-piperazinedione **3** is described.

Ecteinascidins are exceedingly potent antitumor agents isolated from the Caribbean tunicate *Ecteinascidia turbinata*.<sup>1</sup> They are tetrahydroisoquinoline derivatives that are structurally related to safracins and saframycins from microbes (Figure 1). Their novel and diverse structure invites the chemist to explore general approaches to their construction.<sup>2</sup>

We have reported preparation of the ABC ring model compound (**6**) from **3** via **4**.<sup>3</sup> However, a more efficient synthetic route was required, because the overall yield of **6** was low (1.4-1.7%) and this sequence could not be used in the total synthesis of ecteinascidins (Figure 2). The most serious problem was the introduction of the hydroxyl group at the C-10 position at a late stage (*ex*: **5** to **6**). We report here an improved synthesis of **6** from **3** via the useful intermediate (**8**) having a phenolic hydroxyl group at an early stage in eleven steps.

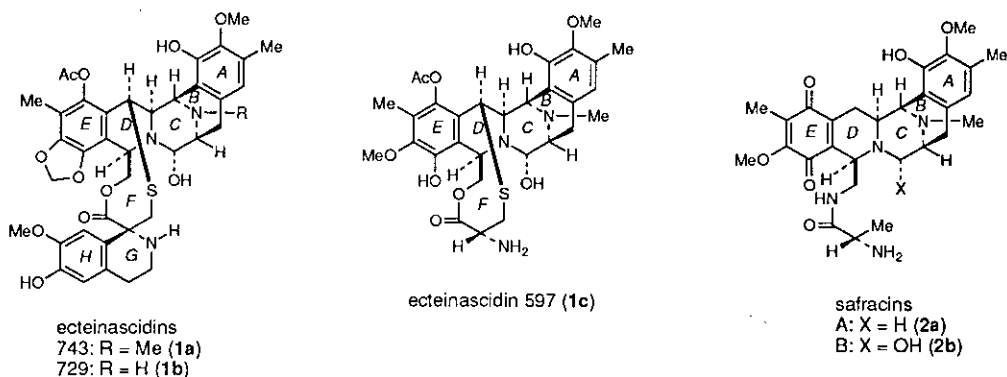
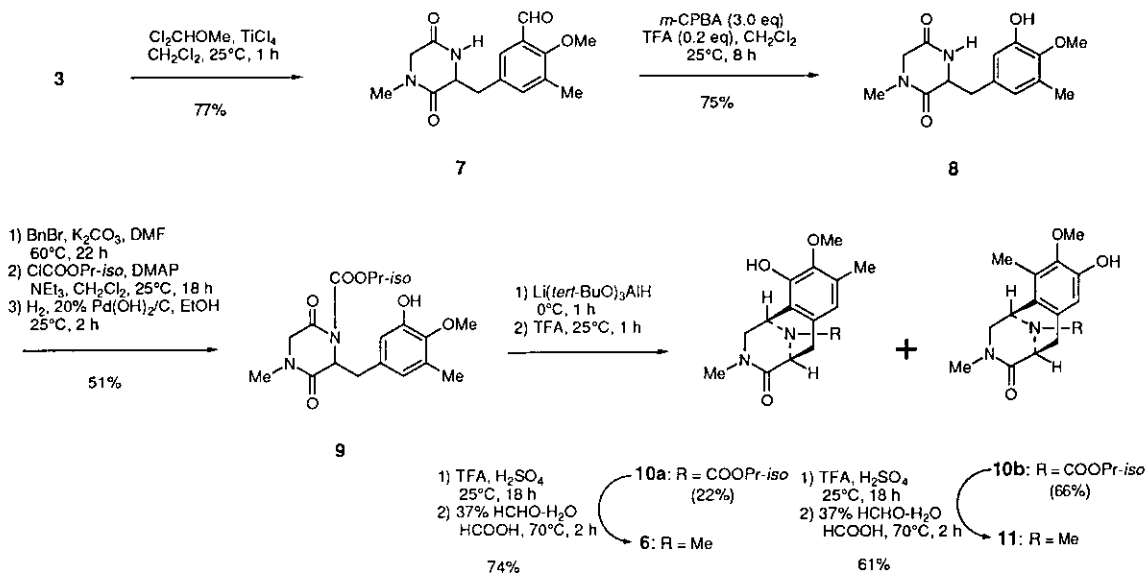
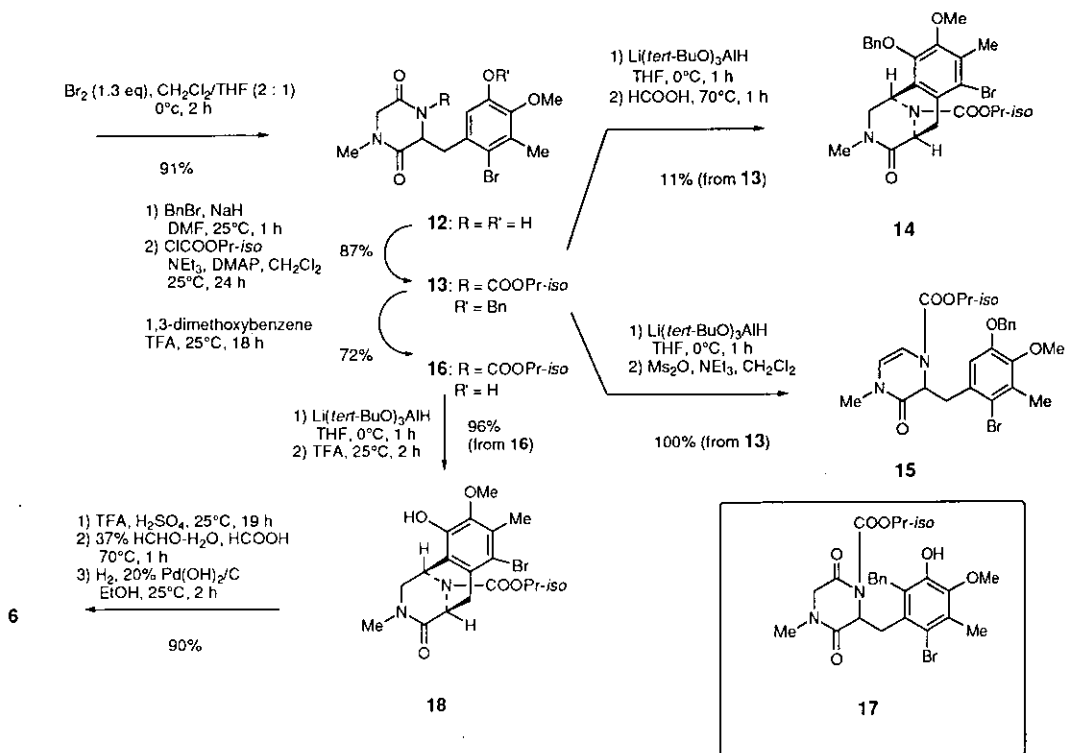


Figure 1





Scheme 1



Scheme 2

efforts to convert **15** to **14** were all unsuccessful. This problem was solved using a phenol intermediate (**16**). Debenzylation of **13** with TFA in 1,3-dimethoxybenzene at 25°C for 18 h gave the phenol (**16**) (amorphous powder; 72%) along with **17**<sup>8</sup> (mp 256-257°C; 21%). Reduction of **16** with an excess of lithium tri-*tert*-butoxyaluminumhydride in THF followed by cyclization with TFA as above afforded **18** (mp 265-266°C) in 96% yield. The protecting group of **18** was cleaved with TFA and H<sub>2</sub>SO<sub>4</sub> at 25°C for 19 h, and the resulting secondary amine was alkylated to the *N*-methyl compound, which was then debrominated to give the final product (**6**) in 88% overall yield. The overall yield of **6** from **3** was 30%. In summary, we have succeeded in an improved synthesis of the ABC ring model of ecteinascidins.

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  4. All structural assignments were carried out by <sup>1</sup>H- and <sup>13</sup>C-NMR, IR, and MS. The molecular composition of the compounds was determined by elemental analysis or HRMS.
  5. See: H. -J. Knölker and W. Fröhner, *Tetrahedron Lett.*, 1997, **38**, 4051. Baeyer-Villiger oxidation was carried out in the absence of a protic acid to give **8** in maximum yield of 20%. When another protic acid (0.2 eq) was used in this reaction, the phenol (**8**) was also obtained with lower yield: TsOH-H<sub>2</sub>O (30%); TfOH (38%); CSA (25%).
  6. For a closely similar, successful cyclization using a brominated compound in total synthesis of (±)-quinocarcin, see: T. Fukuyama and J. J. Nunes, *J. Am. Chem. Soc.*, 1988, **110**, 5196.
  7. Other products [**19** (mp, 113-115°C; 2%) and **20** (mp 222-224°C, 2%)] were obtained. In the <sup>1</sup>H NMR spectra of **19**, when H-7 (δ 6.63) was irradiated, *nOe* (8.3%) of the methyl protons at δ 2.25 was observed. On the other hand, this *nOe* was negligible in the spectra of **12**. These results indicated that **12** was a *para*-brominated compound and **19** was an *ortho*-brominated compound.
  8. As a preliminary experiment, debenzylation of **13** in TFA gave **16** (52%) and **17** (31%). Treatment of **13** with trimethylsilyl iodide (1.5 eq) in chloroform at 50°C for 24 h gave **16** (18%) and **21** (mp 206-208°C; 28%); see: E. H. Vickery, L. F. Pahlter, and E. J. Eisenbraun, *J. Org. Chem.*, 1979, **44**, 2444.

