AN IMPROVED SYNTHESIS OF THE ABC RING MODEL OF ECTEINASCIDINS

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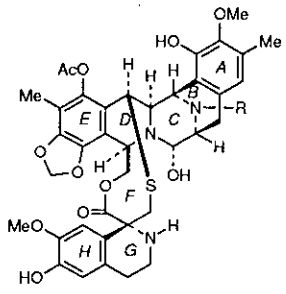
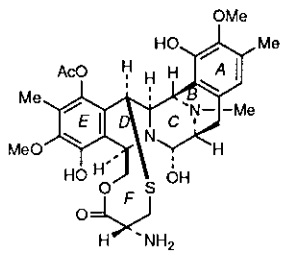
Abstract – An improved synthesis of 1,2,3,4,5,6-hexahydro-1,5-imino-9-methoxy-3,8,11-trimethyl-4-oxo-3-benzazocine (**6**) as an ABC ring model compound of ecteinascidins from 3-(4-methoxy-3-methylphenylmethyl)-1-methyl-2,5-piperazinedione **3** is described.

Ecteinascidins are exceedingly potent antitumor agents isolated from the Caribbean tunicate *Ecteinascidia turbinata*.[1] 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.[2]

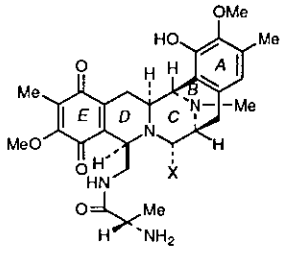
We have reported preparation of the ABC ring model compound (**6**) from **3** *via* **4**.[3] However, a more efficient synthetic route was required, because the overall yield of **6** was low (1.4-1.7%) and this sequence could not be used in the total synthesis of ecteinascidins (Figure 2). The most 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.



ecteinascidins
743: R = Me (**1a**)
729: R = H (**1b**)

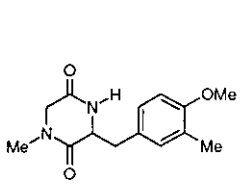


ecteinascidin 597 (**1c**)



safracins
A: X = H (**2a**)
B: X = OH (**2b**)

Figure 1



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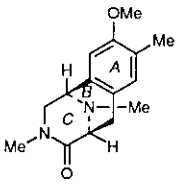

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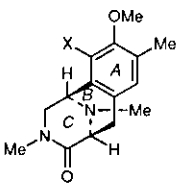

5a: X = NH_2
5b: X = CHO
5c: X = Br

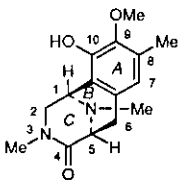

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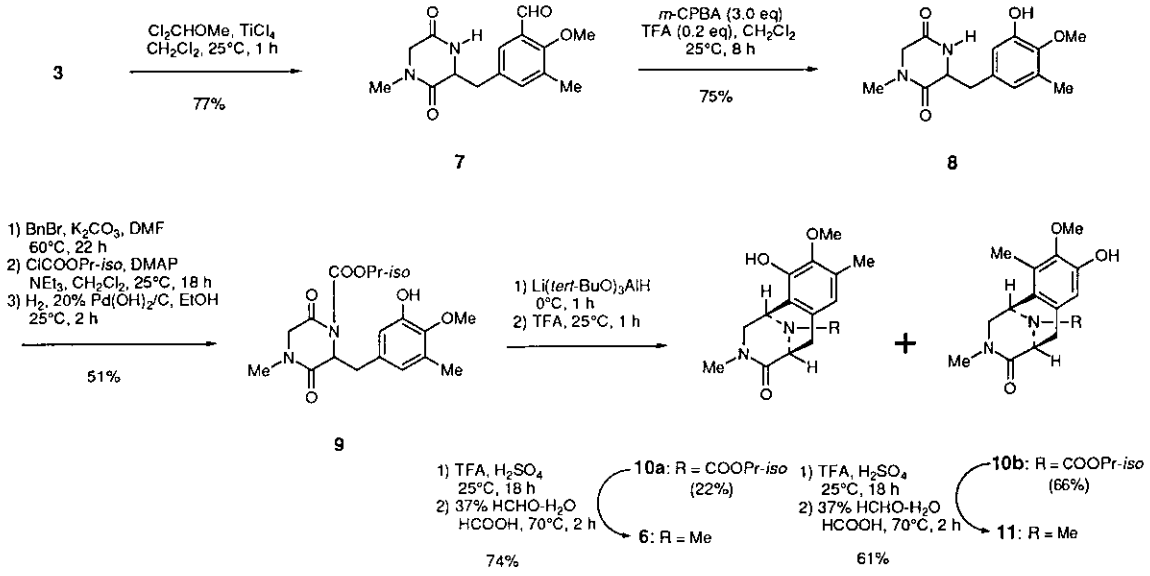
Figure 2

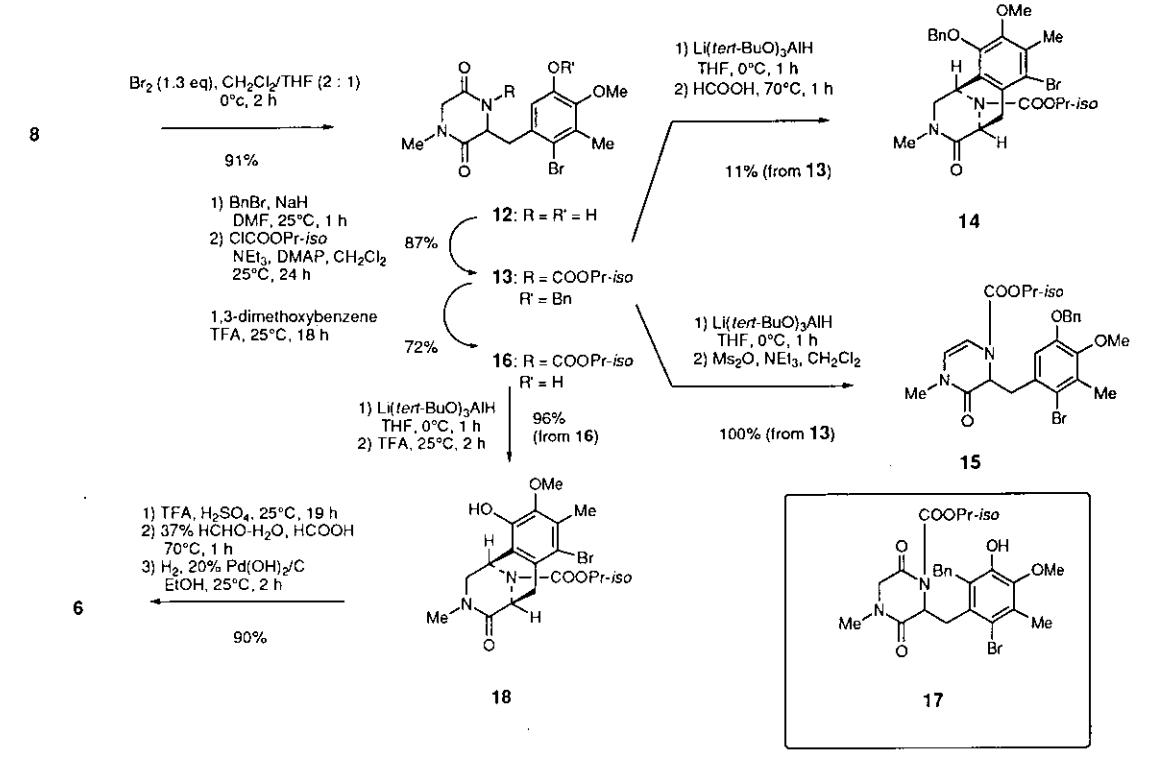
Titanium tetrachloride promoted formylation of **3** afforded the benzaldehyde (**7**)[4] (mp 148-150°C) which was transformed into the phenol (**8**) (mp 199-201°C) by proton-catalyzed Baeyer-Villiger oxidation (Scheme 1).[5] Protection of the phenol (**8**) with benzyl bromide and K_2CO_3 in DMF afforded the *O*-benzylated compound which was transformed by introduction of an isopropyloxycarbonyl group followed by hydrogenolysis to **9** in 51% overall yield.

Compound (**9**) was reduced by an excess of lithium tri-*tert*-butoxyaluminohydride in THF followed by cyclization with TFA at 25°C for 1 h to afford two products which were separated by column chromatography to give **10a** (mp 237-239°C) and **10b** (mp 206-207°C) in 22% and 66% yields, respectively. The regiochemistry of **10a** and **10b** was undetermined at this stage, because the signals in ^{1}H NMR spectra of **10a** and **10b** were not split, which indicated that they were a mixture of two rotational isomers. Conversion of **10a** to the final product (**6**) (mp 216.5-218°C) was accomplished using deprotection with TFA and H_2SO_4 at 25°C followed by reductive methylation in 74% overall yield. Similarly, **10b** was converted to **11** (mp 223-225°C) in 61% yield. Structural assignment of the tricyclic lactams (**6**) and (**11**) was made by ^{1}H NMR analysis. In the ^{1}H NMR spectra of **6**, when H-7 (δ 6.47) was irradiated, nuclear Overhauser enhancement (*nOe*) (10%) of the methyl protons at δ 2.25 was observed, while this *nOe* was negligible in the spectra of **11**.

The yield of this process was low because of the formation of an unwanted para-cyclized product (**10b**). This prompted us to examine the introduction of a bromine to block the para position (Scheme 2).[6] The selective bromination of **8** was effective with bromine in dichloromethane-THF (2:1) at 0°C for 2 h and gave the desired para-brominated compound **12** (mp 232-234°C) in 91% yield.[7] The structure of **12** was supported by the ^{1}H NMR spectrum, and the *nOe* was negligible between the aromatic proton at δ 6.76 and methyl protons at δ 2.37. A two step conversion of **12** to the imide gave **13** in 87% yield. Reduction of **13** with lithium tri-*tert*-butoxyaluminohydride in THF afforded a diastereomeric mixture of the alcohol, which on treatment with formic acid gave **14** (amorphous powder) with a maximum yield of only 11%. When this dehydration/cyclization reaction run with methanesulfonic anhydride and triethylamine in CH_2Cl_2, the desired cyclized compound (**13**) could not be isolated, and instead, enamine (**15**) (mp 125-126°C) was formed in quantitative yield. Numerous



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**[8] (mp 256-257°C; 21%). Reduction of **16** with an excess of lithium tri-*tert*-butoxyaluminohydride 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_2SO_4 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.

ACKNOWLEDGMENTS

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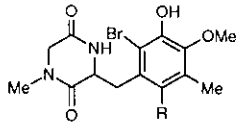
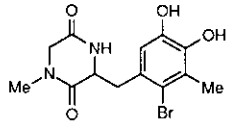
2. For previous work on the synthesis of the saframycins, see: A, Kubo and N. Saito, 'Synthesis of Isoquinolinequinone Antibiotics', in Studies in Natural Products Chemistry, Vol. 10, ed. by Atta-ur-Rahman, Elsevier, Amsterdam, 1992, pp. 77-145. An elegant total synthesis of ecteinascidin 743 was recently reported; E. J. Corey, D. Y. Gin, and R. S. Kania, J. Am. Chem. Soc., 1996, **118**, 9202.
3. a) N. Saito, Y. Obara, M. Azumaya, and A. Kubo, Chem. Pharm. Bull., 1992, **40**, 2620; b) N. Saito, Y. Obara, T. Aihara, S. Harada, Y. Shida, and A. Kubo, Tetrahedron, 1994, **50**, 3915.
4. All structural assignments were carried out by ^{1}H- and ^{13}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_2O (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 ^{1}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. Pahler, and E. J. Eisenbraun, J. Org. Chem., 1979, **44**, 2444.



19: R = H
20: R = Br



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