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.

![Chemical structures](image)

**Figure 1**
Titanium tetrachloride promoted formylation of 3 afforded the benaldehyde (7) (mp 148-150°C) which was transformed into the phenol (8) (mp 199-201°C) by proton-catalyzed Baeyer-Villiger oxidation (Scheme 1). Protection of the phenol (8) with benzyl bromide and K₂CO₃ in DMF afforded the O-benzylated compound which was transformed by introduction of an isopropyloloxycarbonyl 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 ¹H 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 H₂SO₄ 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 ¹H NMR analysis. In the ¹H 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). 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. The structure of 12 was supported by the ¹H 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 CH₂Cl₂, 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

1) BnBr, K₂CO₃, DMF
2) COOPr-iso, DMAP
3) H₂, 20% Pd(OH)₂/C, EtOH
25°C, 2 h

Scheme 2

1) Li(tert-BuO)₂AlH
THF, 0°C, 1 h
2) HCOOH, 70°C, 1 h
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 178 (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 263-266°C) in 96% yield. The protecting group of 18 was cleaved with TFA and H2SO4 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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REFERENCES AND NOTES
4. All structural assignments were carried out by 1H- and 13C-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-H2O (30%); TIOH (38%); CSA (25%).
7. Other products [19 (mp, 113-115°C; 2%) and 20 (mp 222-224°C, 2%)] were obtained. In the 1H 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.

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