

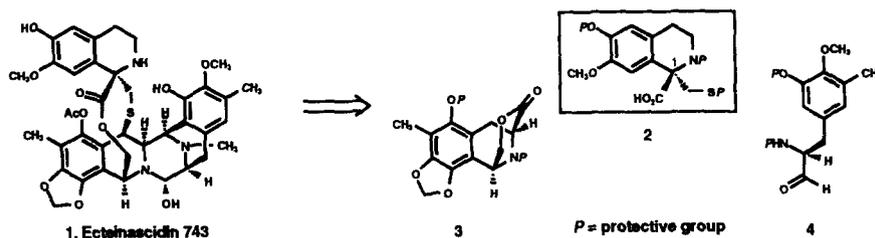
A Convergent Enantioselective Synthesis of the Tetrahydroisoquinoline Unit in the Spiro Ring of Ecteinascidin 743

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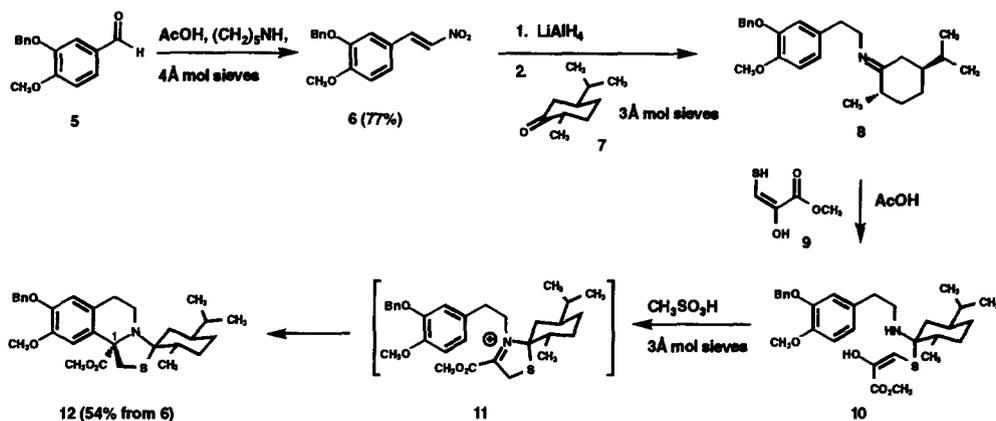
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Summary: An efficient enantioselective synthesis of the spiro tetrahydroisoquinoline unit in ecteinascidin 743 is described, employing (+)-tetrahydrocarvone as a readily available and recoverable chiral auxiliary. The synthetic sequence involves a triply-convergent stereoselective bisannulation to construct the tetrahydroisoquinoline framework within **2**.
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The ecteinascidins make up a family of rare marine-derived alkaloids that exhibit unusually potent *in vivo* antitumor activity and are currently in preclinical development.¹ Structurally the members of this family, exemplified by ecteinascidin 743 (**1**), incorporate a piperazine-bridged bis(tetrahydroisoquinoline) framework similar to that of the saframycin class of antitumor antibiotics.² Unique to the ecteinascidins is the presence of a bridged ten-membered lactone that incorporates a benzylic sulfide linkage and, in the case of **1**, a third spiro tetrahydroisoquinoline unit. In connection with our efforts directed toward the enantioselective synthesis of the ecteinascidins, the tetrahydroisoquinoline subunit **2**, the bridged lactone intermediate **3** and the *N*-protected α -amino aldehyde **4** were envisioned to function as the key intermediates in the construction of the tris(tetrahydroisoquinoline) structure within **1**. Herein is described a short, convergent and enantioselective synthesis of **2** employing tetrahydrocarvone as a readily available and recoverable chiral auxiliary.



The preparation of tetrahydroisoquinoline **2** commenced with 3-benzyloxy-4-methoxybenzaldehyde **5**, which was subjected to nitroaldol condensation (CH_3NO_2 , piperidine, AcOH) to afford nitrostyrene **6** (77%). Reduction of **5** with 3 equiv of LiAlH_4 in THF at 23 °C for 7 h yielded 2-(3-benzyloxy-4-methoxy)phenethylamine which was immediately condensed with 2 equiv of (–)-tetrahydrocarvone **7**³ (C_7H_8 , 55 °C, 3 Å mol sieves, 2 h) to afford the Schiff base **8**. The crude imine was treated with 2 equiv of methyl 3-mercaptopyruvate (**9**)⁴ in the presence of 2 equiv of acetic acid at 23 °C to promote diastereoselective axial thiol



addition to form the *N,S*-ketal **10**. This adduct was directly subjected to cyclization using 2 equiv of methanesulfonic acid under dehydrating conditions (3Å mol sieves, CH_2Cl_2 , 23 °C, 16 h) to effect initial iminium formation (*i.e.*, **11**) and subsequent electrophilic substitution on the aromatic ring to yield tetrahydroisoquinoline **12** (54% from **6**; 6.5:1 mixture of diastereomers, epimeric at C1; ratio invariant with time). It had been expected that the cyclization would generate **2** (with the desired C1-*R* configuration) by preferred approach of the aromatic moiety to the less hindered face of the iminium group in **11** (*i.e.*, *trans* to the adjacent equatorial methyl substituent). However, NOE data⁵ and single crystal X-ray analysis (Figure 1)⁶ of the cyclization product revealed that the major diastereomeric component was the C1-*S* diastereomer **12** in which the methyl ester is *trans* to the equatorial methyl group in the chiral auxiliary. Thus, it appears that the second ring closure in the transformation of **10** → **12** is an example of a Pictet-Spengler type cyclization that proceeds through a late (product resembling) transition state in which the iminium carbon in **11** is significantly pyramidalized.

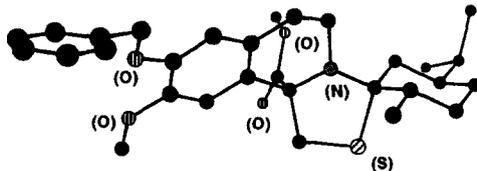
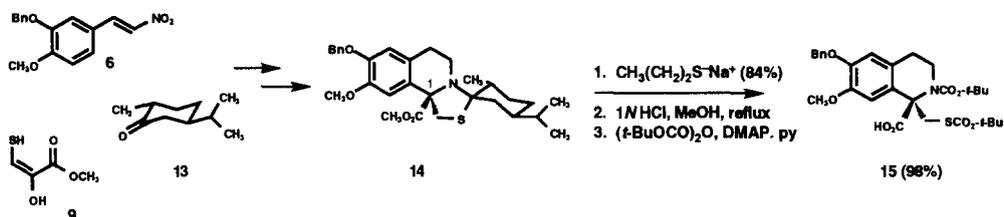


Figure 1. X-ray Crystal Structure of **12**.

Generation of the enantiomer of **12** thus became straightforward, and was accomplished using (+)-tetrahydrocarvone **13**³ as the chiral auxiliary. Condensation of **13** with the intermediates **6** and **9** using the same reaction sequence outlined above⁷ gave the tetrahydroisoquinoline product **14** as the principal cyclized product in comparable yield and diastereoselectivity. Selective cleavage of the methyl ester function in **14** was accomplished by reaction with 4 equiv of sodium *n*-propylmercaptide in DMF at 45 °C for 3 h to yield the corresponding carboxylic acid. It is worthy to note that although **14** was formed as a chromatographically inseparable mixture of

C1-epimers, the desired C1-*R* diastereomer underwent ester deprotection faster than its C1-*S* counterpart, presumably a result of steric shielding of the methyl ester group by the equatorial methyl substituent on the tetrahydrocarvone ring system in C1-*epi*-14. Thus, quenching of the ester cleavage reaction at *ca.* 85%



conversion afforded the free carboxylic acid exclusively as the single desired diastereomer in 84% yield. The final steps in the sequence included acid hydrolysis (1 *N* HCl in MeOH, reflux, 3.5 h) followed by hexane extraction of the reaction mixture to isolate the chiral auxiliary **13** with quantitative recovery. The resulting tetrahydroisoquinoline carboxylic acid was directly treated with 4 equiv of di-*tert*-butylpyrocarbonate and DMAP (0.8 equiv) in pyridine resulting in *N*- and *S*- acylation to afford, after silica gel chromatography, acid **15** (98% yield), suitable for esterification with appropriate synthetic pentacyclic intermediates in the synthesis of **1**.

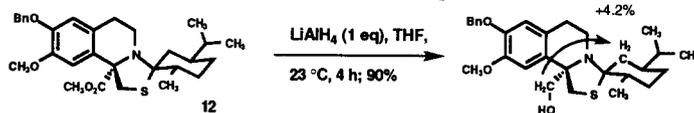
In summary, an efficient enantioselective synthesis of the spiro tetrahydroisoquinoline unit in ecteinascidin **743** is described, which employs (+)-tetrahydrocarvone as a chiral controller and which follows an unexpected and unusual stereochemical course. The key feature of the synthetic sequence involved a triply-convergent stereoselective bisannulation employing the intermediates **6**, **9** and **13** to give, after deprotection, the selectively protected tetrahydroisoquinoline product **15**. The strategy outlined in the synthesis of **15** may facilitate synthetic access not only to members of the ecteinascidin antitumor agents, but also to a host of related structures of potential biological utility. An enantioselective total synthesis of ecteinascidin **743** (**1**) has recently been completed.^{8,9}

References and Notes

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- For previous work on the synthesis of the saframycins see: (a) Fukuyama, T.; Sachleben, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 4957. (b) Fukuyama, T.; Yang, L.; Ajeck, K. L.; Sachleben, R. A. *J. Am.*

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- The (-) and (+) enantiomers of tetrahydrocarvone (**12** and **13**) were prepared from (+) and (-)-carvone, respectively, by a two-step reduction procedure followed by epimerization of the α -Me group (3 atm H₂, cat. Rh(PPh₃)₃Cl, C₆H₆, 23 °C, 23 h; 1 atm H₂, MeOH, cat. 10% Pd-C, 23 °C, 2.5 h; NaOMe, MeOH, 23 °C, 18 h) to minimize double bond transposition and concomitant racemization. Rotations: $[\alpha]_D^{23}$ for **12** = -15.5 and for **13** = +15.5 (c=3, EtOH).
- The method of preparation of **9** was analogous to that described for ethyl 3-mercaptopyruvate: Taylor, E. C.; Reiter, L. A. *J. Am. Chem. Soc.* **1989**, *111*, 285.
- NOE experiments were performed on the LiAlH₄ reduction product of **12**:



- Crystal structure solved by Dr. Axel Fischer.

7. Preparation of 14: To a solution of **6** (173 mg, 0.608 mmol, 1 equiv) in THF (6 mL), at -78 °C was added solid LiAlH₄ (69 mg, 1.82 mmol, 3.0 equiv), and the resulting suspension was stirred at 23 °C for 7 h before the excess reducing agent was quenched with the sequential dropwise addition of water (69 μ L), 3 N aqueous sodium hydroxide solution (69 μ L), and water (210 μ L) at 0 °C. The suspension was diluted with EtOAc (20 mL), and the solids were removed by filtration. The filtrate was concentrated, and a suspension of the crude amine, **13** (188 mg, 1.22 mmol, 2.0 equiv), and crushed activated 4 Å molecular sieves (~550 mg) in toluene (2.5 mL) was stirred at 55 °C for 2 h. The reaction mixture was allowed to cool to 23 °C prior to the sequential addition of solid **9** (163 mg, 1.22 mmol, 2.0 equiv) and acetic acid (35 μ L, 0.608 mmol, 1.0 equiv). The mixture was stirred at 23 °C for 2 h, then was diluted with EtOAc (50 mL). The mixture was washed sequentially with saturated aqueous NaHCO₃ solution (50 mL) and saturated aqueous NaCl solution (50 mL), and then was dried (Na₂SO₄) and concentrated. The residue was dissolved in CH₂Cl₂ (30 mL), and to this solution was added crushed activated 3 Å molecular sieves (~1 g) and CH₃SO₃H (79 μ L, 1.22 mmol, 2.0 equiv). The mixture was stirred at 23 °C for 16 h and then filtered. The filtrate was washed with saturated aqueous NaHCO₃ solution (30 mL) and saturated aqueous NaCl solution (30 mL), and then was dried (Na₂SO₄) and concentrated. The residue was purified by filtration through a plug of silica gel (10% EtOAc in CH₂Cl₂ eluent) followed by flash column chromatography (10% EtOAc in hexanes) to give **14** (167 mg, 54% 4 steps) as a 6.5:1 mixture of diastereomers at C1. R_f 0.18 (10% ethyl acetate in hexanes); $[\alpha]_D^{23}$ = +116 (c = 0.30, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ 7.46 (m, 2H), 7.40 (m, 2H), 7.33 (m, 1H), 6.90 (s, 1H), 6.66 (s, 1H), 5.12 (s, 2H), 3.86 (s, 3H), 3.77 (d, 1H, J = 9.7 Hz), 3.77 (m, 1H), 3.63 (s, 3H), 3.10 (dd, 1H, J = 6.8, 12.1 Hz), 2.87 (m, 1H), 2.64 (d, 1H, J = 9.7 Hz), 2.61 (m, 1H), 1.93 (m, 1H), 1.72 (m, 2H), 1.61 (m, 2H), 1.51 (m, 1H), 1.43 (m, 1H), 1.24 (m, 2H), 0.85 (m, 9H); FTIR (neat film) 2955 (s), 2930 (s), 1724 (s), 1511 (s), 1463 (m), 1446 (m), 1368 (m), 1259 (s), 1241 (s), 1214 (s), 1164 (s), 1018 (m), 1001 (m) (cm⁻¹); HRMS (CI⁺) m/z : Calcd for C₃₀H₄₀NO₄S (MH⁺) 510.2678, found 510.2700.

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