Pergamon

Tetrahedron Letters, Vol. 37, No. 40, pp. 7163-7166, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01622-X

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

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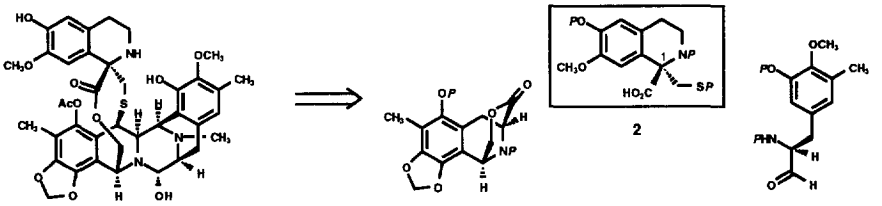
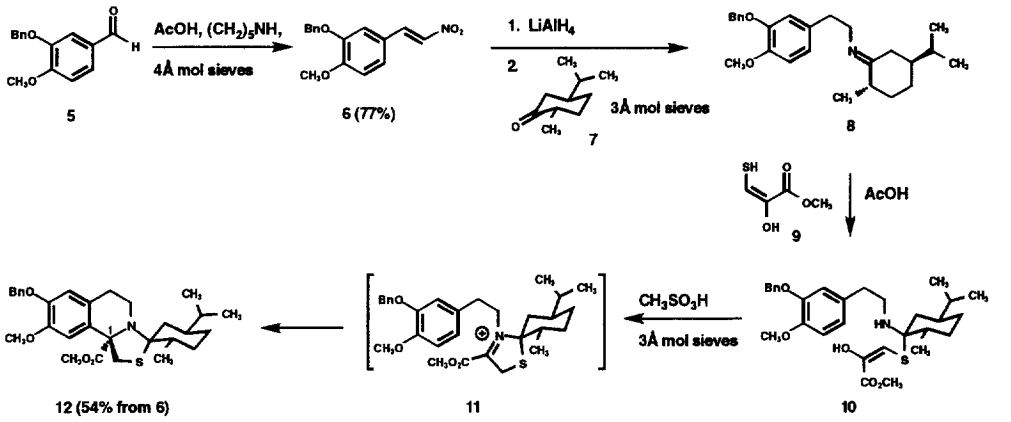
Summary: *An efficient enantioselective synthesis of the spiro tetrahydroisoquinoline unit in ecteinascidin 743 is described, employing (+)-tetrahydrocarvone as a readily available and recoverable chiral auxiliary. The synthetic sequence involves a triply-convergent stereoselective bisannulation to construct the tetrahydroisoquinoline framework within* ***2****.*

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, 3Å 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 data[5] 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.

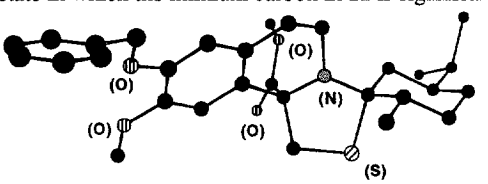
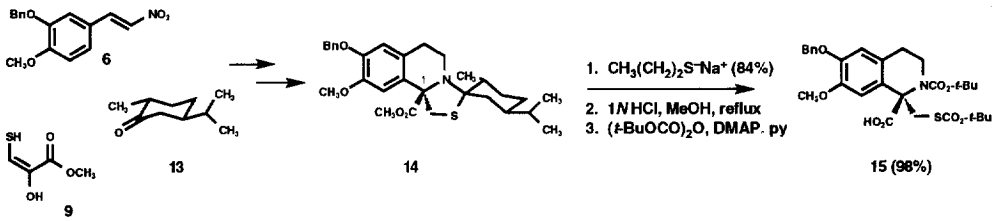


Figure 1. X-ray Crystal Structure of 12.

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 above[7] 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

1 (a) Rinehart, K. L.; Shield, L. S. in *Topics in Pharmaceutical Sciences*, eds. Breimer, D. D.; Crommelin, D. J. A.; Midha, K. K. (Amsterdam Medical Press, Noordwijk, The Netherlands), 1989, pp. 613. (b) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Keifer, P. A.; Wilson, G. R.; Perun, T. J., Jr.; Sakai, R.; Thompson, A. G.; Stroh, J. G.; Shield, L. S.; Seigler, D. S.; Li, L. H.; Martin, D. G.; Grimmelikhuijzen, C. J. P.; Gäde, G. *J. Nat. Prod.* **1990**, *53*, 771. (c) Rinehart, K. L.; Sakai, R; Holt, T. G.; Fregeau, N. L.; Perun, T. J., Jr.; Seigler, D. S.; Wilson, G. R.; Shield, L. S. *Pure Appl. Chem.* **1990**, *62*, 1277. (d) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Stroh, J. G.; Keifer, P. A.; Sun, F.; Li, L. H.; Martin, D. G. *J. Org. Chem.* **1990**, *55*, 4512. (e) Wright, A. E.; Forleo, D. A.; Gunawardana, G. P.; Gunasekera, S. P.; Koehn, F. E.; McConnell, O. J. *J. Org. Chem.* **1990**, *55*, 4508. (f) Sakai, R.; Rinehart, K. L.; Guan, Y.; Wang, H.-J. *Proc. Natl. Acad. Sci. USA* **1992**, *89*, 11456.

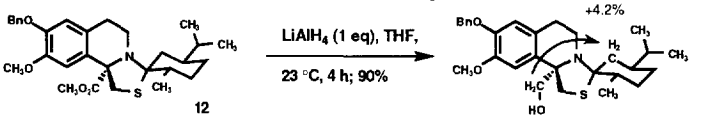
2. For previous work on the synthesis of the saframycins see: (a) Fukuyama, T.; Sachleben, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 4957. (b) Fukuyama, T.; Yang, L.; Ajeck, K. L.; Sachleben, R. A. *J. Am.*

Chem. Soc. **1990**, *112*, 3712. (c) Saito, N.; Yamauchi, R.; Nishioka, H.; Ida, S.; Kubo, A. *J. Org. Chem.* **1989**, *54*, 5391.

3. 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 H_2, cat. $Rh(PPh_3)_3Cl$, C_6H_6, 23 °C, 23 h; 1 atm H_2, 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).

4. 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.

5. NOE experiments were performed on the $LiAlH_4$ reduction product of **12**:



6. 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 $LiAlH_4$ (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 μL), 3 *N* aqueous sodium hydroxide solution (69 μL), and water (210 μL) 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 μL, 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 $NaHCO_3$ solution (50 mL) and saturated aqueous NaCl solution (50 mL), and then was dried (Na_2SO_4) and concentrated. The residue was dissolved in CH_2Cl_2 (30 mL), and to this solution was added crushed activated 3 Å molecular sieves (~1 g) and CH_3SO_3H (79 μL, 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 $NaHCO_3$ solution (30 mL) and saturated aqueous NaCl solution (30 mL), and then was dried (Na_2SO_4) and concentrated. The residue was purified by filtration through a plug of silica gel (10% EtOAc in CH_2Cl_2 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, CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) 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 $C_{30}H_{40}NO_4S$ (MH^+) 510.2678, found 510.2700.

8. Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* submitted.

9. This research was assisted financially by the National Institutes of Health and a Canadian NSERC fellowship to DYG.

(*Received in USA* 19 *July* 1996; *revised* 9 *August* 1996; *accepted* 12 *August* 1996)