Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 7091–7094

TETRAHEDRON LETTERS

A new efficient synthetic process for the construction of the pentacyclic core of marine alkaloid ecteinascidins

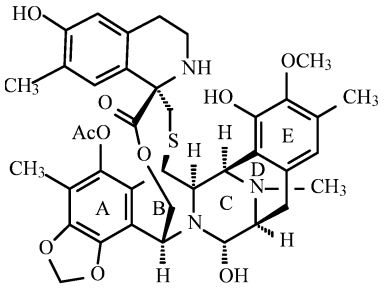
Ye-Feng Tang, Zhan-Zhu Liu* and Shi-Zhi Chen

Institute of Materia Medica, Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing 100050, PR China

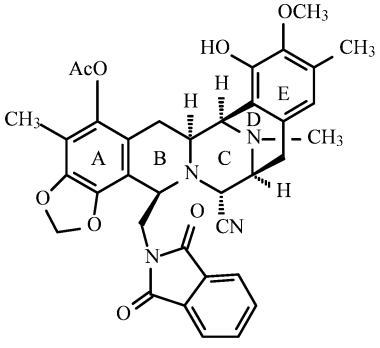
Received 13 May 2003; revised 27 June 2003; accepted 14 July 2003

Abstract—The pentacyclic core of ecteinascidins was constructed from two fundamental building blocks, the 1,2,3,4-tetrahydroisoquinoline derivative and the substituted phenylalanine derivative, via 8 steps using readily available L-Dopa as starting material. The key steps involve coupling of the two aforementioned building blocks, regioselective reduction of the 11-carbonyl group of the key intermediate piperazine-1,4-dione derivative, and intramolecular Pictet–Spengler cyclization.

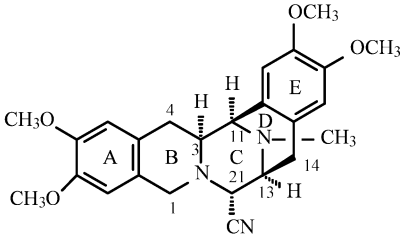
Ecteinascidins are a family of marine-derived tetrahydroisoquinoline alkaloids, which possess extremely potent antitumor activity.[1] Ecteinascidin 743 (Et 743, **1**), the most abundant and bioactive of this family, is being studied in phase I/II clinical trials.[2] Much synthetic effort has been directed towards the synthesis of Et 743,[3] but due to its formidable structural complexity, there have been only three successful results reported so far by Corey, Cuevas and Fukuyama groups, respectively.[4] Fortunately, phthalascidin (Pt 650, **2**), a structurally simplified version of **1**, was found to exhibit comparable antitumor activity to that of Et 743 and may therefore be a more practical therapeutic agent.[5] In view of the structural feature, the cores of both **1** and **2** are characterized by a bis(tetrahydroisoquinoline) pentacyclic system (ABCDE), which is believed to be the primary pharmacophore through the preliminary structure–activity study of Et 743 and its analogs (Fig. 1).[5] This inspired us to start a research project on the discovery of structurally simplified, synthetically accessible and biologically active ecteinascidin analogs as antitumor agents. In this communication, we report the synthesis of **3** that bears the same pentacyclic framework as that of **1** and **2** via a new efficient synthetic route, which we believe is of considerable value in the synthesis of simplified ecteinascidin analogs.



Et 743 (1)



Pt 650 (2)



3

Figure 1.

Keywords: ecteinascidins; pentacyclic core; L-Dopa; Pictet–Spengler cyclization.
* Corresponding author. Tel.: 86-10-63165253; fax: 86-10-63017757; e-mail: liuzhanzhu@imm.ac.cn

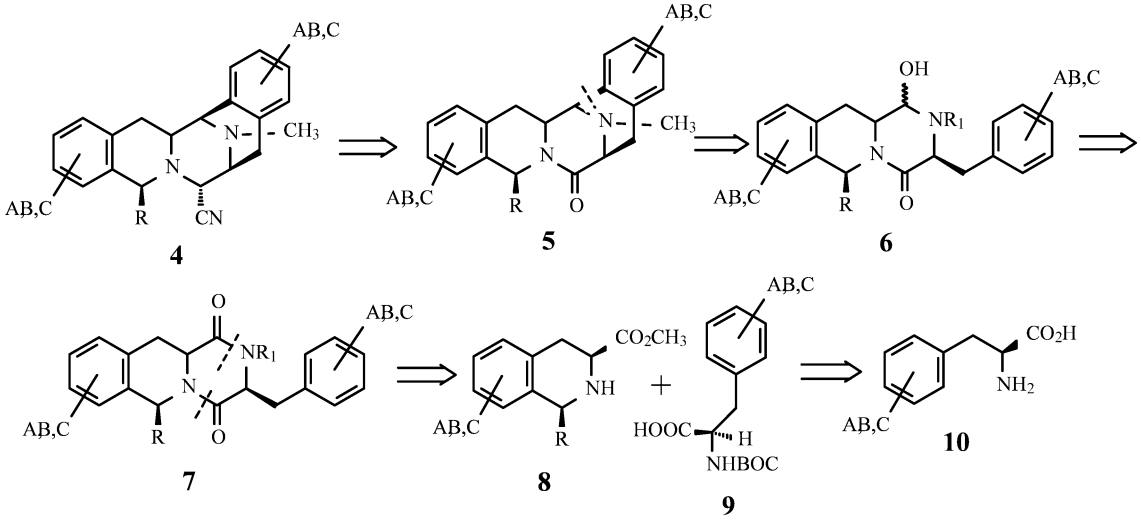
0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01785-4

Retrosynthetic analysis of the pentacyclic core of ecteinascidins leads us to employ an original synthetic strategy different from those reported.[3] According to our design, the BCD-ring system could be constructed sequentially (Scheme 1). Thus, **4** could be derived from **5** through reduction of the 21-carbonyl group followed by replacement of the hydroxyl group with the cyanide group. Compound **5** could be obtained from **6** via an intramolecular Pictet–Spengler cyclization, and **6** maybe accessed by regioselective reduction of the 11-carbonyl group of the piperazine-1,4-dione derivative **7**, a key intermediate in our synthesis. Compound **7**, as we assumed, could be derived from two fundamental building blocks, the 1,2,3,4-tetrahydroisoquinoline derivative **8** and the substituted phenylalanine derivative **9**, via formation of two amide bonds. Both **8** and **9** could be easily obtained from the substituted phenylalanine **10** by several functional group manipulations.

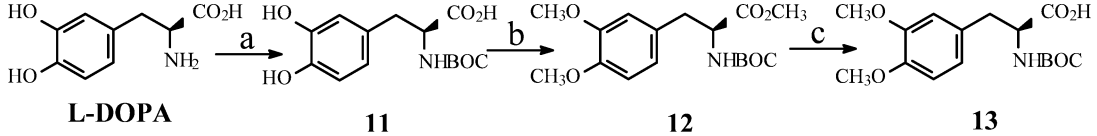
Partly enlightened by the biosynthetic study on ecteinascitins,[6] which supposed that the pentacyclic core of ecteinascidins was derived from two molecules of L-Dopa or L-tyrosine, we chose the commercially available L-Dopa as the starting material. Thus, protection of the amino group of L-Dopa by BOC provided **11**, which was treated with an excess of Me_2SO_4/K_2CO_3 in acetone at reflux to give **12**.[7] Then hydrolysis of **12** in 1N NaOH afforded **13** as one of the two building blocks. The overall yield of **13** from L-Dopa was 70% (Scheme 2).

According to a known method,[8] L-Dopa was submitted to Pictet–Spengler reaction using 37% HCHO in 0.5N H_2SO_4 to yield the 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **14**. Of particular note, formaldehyde was chosen here for convenience. We have investigated a series of aliphatic and aromatic aldehydes in this reaction to produce the corresponding 1-substituded tetrahydroisoquinoline derivatives. In each case, the 1,3-*cis* isomer was obtained as the major product.[9] Thus, it is feasible to introduce a desired stereocenter on the 1-postion of the pentacyclic core via an asymmetric Pictet–Spengler reaction when needed. Esterification of **14** in HCl/CH_3OH at reflux provided **15**. Protection of the nitrogen of **15** by a formyl group afforded **16**, which was transformed into the methylation product **17** upon treatment with Me_2SO_4/K_2CO_3 in acetone at reflux. Cleavage of the formyl group in HCl/CH_3OH provided another building block **18**.[10] The overall yield of **18** from L-Dopa is ca. 50% (Scheme 3).

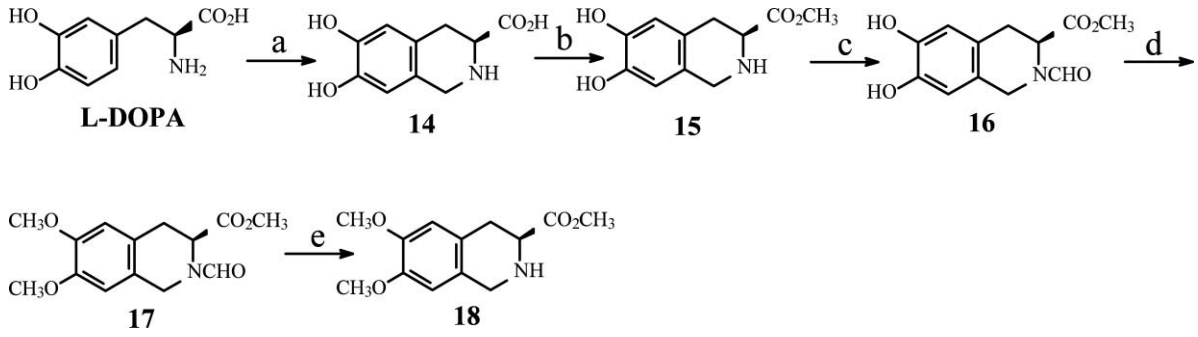
Coupling of **13** and **18** to form **19** was accomplished through the action of bis(2-oxo-3-oxazolidinyl) phosphinic chloride (BOP-Cl) in 80% yield. Then **19** was treated with CF_3CO_2H in CH_2Cl_2 to afford the key intermediate piperazine-1,4-dione derivative **20**, which was converted to the carbamate **21** in 80% yield according to a known procedure.[11] Regioselective reduction of 11-carbonyl group of **21** with an excess amount of $Li(t\text{-}BuO)_3AlH$ in THF provided the diastereomeric mixture of the alcohol **22**, which, on treatment with HCO_2H at 70°C, yielded exclusively the expected pentacyclic framework of ecteinascidins **23**. It is worth noting that a compound similar to **23** was committed to the same cyclization condition by another research team,



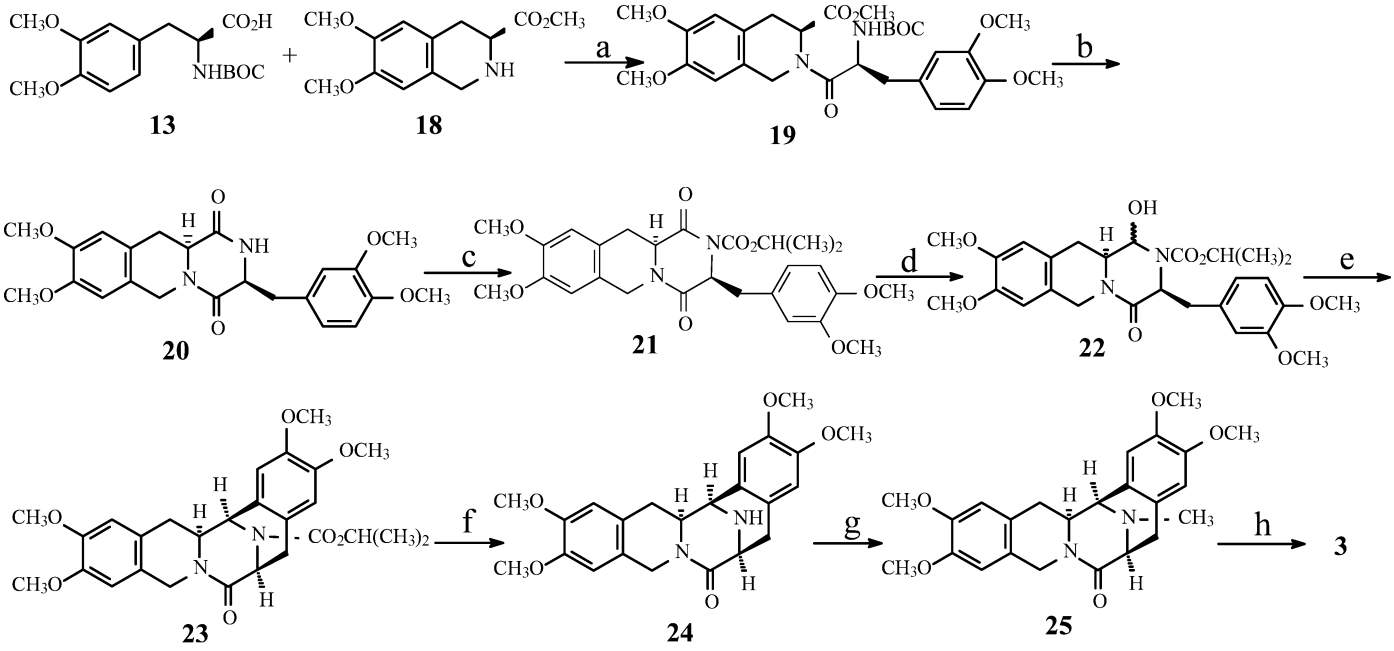
Scheme 1.



Scheme 2. *Reagents and conditions*: (a) $(Boc)_2O$, Et_3N, DMF, 60°C, 89%; (b) Me_2SO_4, K_2CO_3, CH_3COCH_3, reflux, 92%; (c) 1N KOH/CH_3OH, 90%.



Scheme 3. *Reagents and conditions*: (a) HCHO, 0.5N H_2SO_4, 24 h, 75%; (b) HCl/CH_3OH, reflux, 6 h, 99%; (c) Ac_2O/HCO_2H, 4 h; then H_2O/CH_3OH, 87%; (d) Me_2SO_4, K_2CO_3, CH_3COCH_3, reflux, 90%; (e) HCl/CH_3OH, reflux, 4 h, 85%.



Scheme 4. *Reagents and conditions*: (a) BOP-Cl, Et_3N, CH_2Cl_2, 4 h, 80%; (b) CF_3COOH/CH_2Cl_2, 2 h, 86%; (c) $ClCO_2CH(CH_3)_2$, DMAP, Et_3N, CH_2Cl_2, 6 h, 80%; (d) Li(*t*-BuO)$_3$AlH, THF, 0°C, 2 h, then H_2O, 90%; (e) HCO_2H, 70°C, 3 h, 65%; (f) H_2SO_4/CF_3CO_2H, 15 h, 98%; (g) $HCHO/HCO_2H$, 70°C, 2 h, 95%; (h) $LiAlH_4$, THF, −17°C, 0.5 h, then 0°C, 1 h; KCN, phosphate buffer (pH = 7), 2 h, 82%.

but an unsuccessful result was reported.[12] Next, deprotection of **23** with a mixture of CF_3CO_2H and H_2SO_4 gave the secondary amine **24** in quantitative yield. Reductive methylation of **24** with $HCHO/HCO_2H$ at 70°C for 2 h provided **25** in 95% yield. Finally, the lactam ring of **25** could be easily reduced through treatment with an excess of $LiAlH_4$ in THF at 0°C for 1 h to afford the corresponding cyclic hemiaminal, which upon exposure to KCN in phosphate buffer (pH = 7) afforded the pentacyclic amino nitrile **3** as an enantiomerically pure product in 82% overall yield from **25** (Scheme 4).

Gratifyingly, **3** does not only possess the desired pentacyclic core of ecteinascidins, but also bears four completely correct stereocenters (3*S*,11*S*,13*S*,21*R*) as those of the natural products. This conclusion was verified on the basis of its spectroscopic data,[13] especially the NOE difference spectroscopy. Obvious NOE enhancement was observed between H-3 and H-11, thus the *syn* C3–C11 backbone stereochemical relationship was established. Similarly, irradiation of the H-21 produced noticeable NOE enhancement of Hβ-1,but not of Hα-1,which indicated that H-21 was of β-configuration

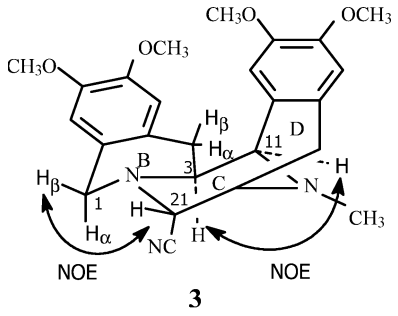


Figure 2.

(Fig. 2). These data are consistent with the stereochemical relationship of the four stereocenters.

In summary, we have developed a new efficient synthetic route for the construction of the pentacyclic core of ecteinascidins starting from L-Dopa. Further study on the synthesis of structurally simplified and bioactive ecteinascidin analogs based on this methodology is ongoing in our laboratory.

References

1. For a review, see: Scott, J. D.; Williams, R. M. *Chem. Rev.* **2002**, *102*, 1669–1730.
2. For clinical data, see: (a) Ryan, D. P.; Supko, J. G.; Eder, J. P.; Seiden, M. V.; Demetri, G.; Lynch, T. J.; Fischman, A. J.; Davis, J.; Jimeno, J.; Clark, J. W. *Clin. Cancer Res.* **2001**, *7*, 231–242; (b) Zelek, L.; Yovine, A.; Etienne, B.; Jimeno, J.; Taamma, A.; Martin, C.; Spielmann, M.; Cvitkovic, E.; Misset, J. L. The American Society of Clinical Oncology, 36th Annual Meeting, New Orleans, May 20–23, 2000; Abstract number 592; (c) Delaloge, S.; Yovine, A.; Taamma, A.; Cottu, P.; Riofrio, M.; Raymond, E.; Brain, E.; Marty, M.; Jimeno, J.; Cvitkovic, E.; Misset, J. L. The American Society of Clinical Oncology, 36th Annual Meeting, New Orleans, May 20–23, 2000; Abstract number 2181; (d) Le Cesne, A.; Judson, I.; Blay, J. Y.; Radford, J.; van Oosterom, A.; Lorigan, P.; Rodenhuis, E.; Donato Di Paoula, E.; Van Glabbeke, M.; Jimeno, J.; Verweij, J. The American Society of Clinical Oncology, 36th Annual Meeting, New Orleans, May 20–23, **2000**; Abstract number 2182; (e) Aune G. J.; Furuta T.; Pommier Y. *Anti-cancer Drugs* **2002**, *13*, 545–555.
3. For some recent examples, see: (a) Saito, N.; Tachi, M.; Seki, R.; Kamayachi, H.; Kubo, A. *Chem. Pharm. Bull.* **2000**, *48*,1549–1557; (b) Endo, A.; Kann, T.; Fukuyama, T. *Synlett* **1999**, 1103–1105; (c) Zhou, B.; Guo J.; Danishefsky, S. J. *Tetrahedron Lett.* **2000**, *41*, 2043–2046; (d) Martinez, E. J.; Corey, E. J. *Org. Lett.* **2000**, *2*, 993–996; (e) Jin, W.; Metobo, S.; Williams, R. M. *Org. Lett.* **2003**, in press.
4. (a) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202–9203; (b) Cuevas, C.; Pérez, M.; Martín, M. J.; Chicharro, J. L.; Fernádez-Rivas, C.; Flores, M.; Francesch, A.; Gallego, P.; Zarzuelo, M.; de la Calle, F.; García, J.; Polanco, C.; Rodríguez, I.; Manzanares, I. *Org. Lett.* **2000**, *2*, 2545–2548; (c) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552–6554.
5. Martinez, E. J.; Owa, T.; Schreiber, S. L.; Corey, E. J. *Proc. Natl. Acad. Sci.* **1999**, *96*, 3496–3501.
6. (a) Kerr, R. G.; Miranda, N. F. *J. Nat. Prod.* **1995**, *58*, 1618–1621; (b) Sakai, R.; Jares-Erijman, E. A.; Manzanares, I.; Elipe, M. V. S.; Rinehart, K. L. *J. Am. Chem. Soc.* **1996**, *118*, 9017–9023.
7. Garciá, E.; Arrasate, S.; Ardeo, A.; Lete, E.; Sotomayor, N. *Tetrahedron Lett.* **2001**, *42*, 1511–1513.
8. Brossi, A.; Focella, A.; Teitel, S. *Helv. Chim. Acta* **1972**, *55*, 15–21.
9. Wang, Y.; Liu, Z. Z.; Chen, S. Z.; Liang, X. T. *Chin. Chem. Lett.* **2003**, in press.
10. Dean, R. T.; Rapoport, H. *J. Org. Chem.* **1978**, *43*, 4183–4189.
11. Kubo, A.; Saito, N.; Yamato, H.; Masubuchi, K.; Nakamura, M. *J. Org. Chem.* **1988**, *53*, 4295–4310.
12. Fukuyama, T.; Sacheben, R. A. *J. Am. Chem. Soc.* **1982**, *104*, 4957–4958.
13. Analytical and spectroscopic data for **3**: light yellow solid; mp 124.5–127°C; $[\alpha]_D^{20}=+19.3$ (*c* 0.4, $CHCl_3$); ^1H NMR (300 Hz, $CDCl_3$): δ 2.35 (s, 3H, -NCH_3), 2.64–2.55 (m, 3H, H-4+H-14), 3.14 (dd, 1H, $J=8.4$, 18.0 Hz, H-4), 3.24–3.18 (ddd, 1H, $J=3.0$, 4.8, 8.4 Hz, H-3), 3.47 (d, 1H, $J=8.1$ Hz, H-13), 3.59 (d, 1H, $J=3.0$ Hz, H-11), 3.71 (d, 1H, $J=15.0$ Hz, Hβ-1), 3.78–3.81 (m, 9H, 3× CH_3O), 3.87 (d, 1H, $J=15.0$Hz, Ha-1), 3.90 (s, 3H, CH_3O), 3.94 (d, 1H, $J=2.1$ Hz, H-21), 6.43 (s, 1H, Ar-H), 6.48 (s, 1H, Ar-H), 6.52 (s, 1H, Ar-H), 6.57 (s, 1H, Ar-H); ^{13}C NMR (300 Hz, $CDCl_3$): δ 25.7, 31.6, 42.0, 54.2, 55.4, 55.8, 55.9, 55.9, 56.3, 56.3, 62.2, 62.4, 108.6, 110.8, 110.9, 113.5, 117.2, 123.5, 123.8, 124.3, 126.1, 146.5, 147.4, 147.7, 148.4; IR (KBr, cm^{-1}): 2220 (CN, w), 1660 (C=O, s); FAB-MS (*m*/*z*): 436 (M+1, 27%), 435 (M, 10%), 409 (22%), 204 (100%); HRMS (FAB): calcd for $C_{25}H_{30}N_3O_4$ (M+1) 436.2236; found 435.2214.