ORGANIC LETTERS

1999
Vol. 1, No. 1
75−77

Enantioselective Synthesis of Saframycin A and Evaluation of Antitumor Activity Relative to Ecteinascidin/Saframycin Hybrids

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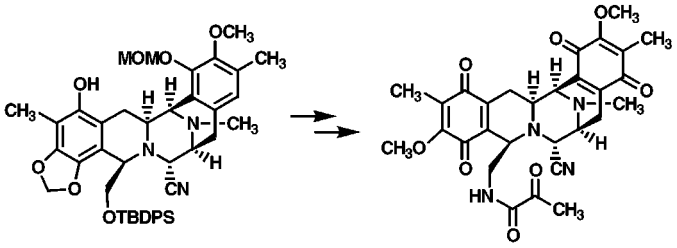
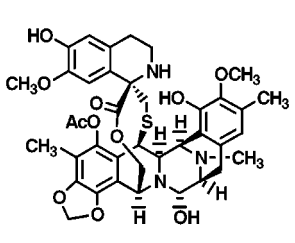
Received April 1, 1999

ABSTRACT

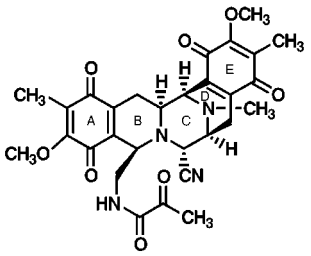


A short synthesis of saframycin A is described which begins with a readily available intermediate previously utilized for the total synthesis of ecteinascidin 743. A key step in this synthesis is the use of 1-fluoro-3,5-dichloropyridinium triflate to oxidize a phenolic ring to a 1,4-benzoquinone unit while simultaneously cleaving a methoxymethyl ether of a different phenolic ring to the corresponding phenol (4 → 5). The common intermediate (2) for the synthesis of saframycin A (1) and ecteinascidin 743 also allowed the synthesis of two hybrids of these structures (6 and 7). Whole cell bioassays for antitumor activity using lung, colon, melanoma, and prostate-derived tumor cell lines allowed a clear correlation of structure with biological activity in this series.

Ecteinascidin 743,[1] an exceedingly potent antitumor agent which is currently undergoing phase II clinical trials, has recently been synthesized by a process[2] that is being applied for the preparation of clinical material. This paper describes a short synthesis of the structurally related antitumor agent saframycin A (**1**)[3] from an intermediate which was utilized in the synthesis of ecteinascidin 743, thus making available a common route for producing both saframycin- and ecteinascidin-type compounds. Syntheses of both racemic and natural forms of saframycin A have previously been reported.[4] In addition, we describe herein the synthesis of two structural hybrids of ecteinascidins and saframycins and the evaluation of antitumor activity for these substances relative to ecteinascidin 743 (Et 743) and saframycin A.



Ecteinascidin 743



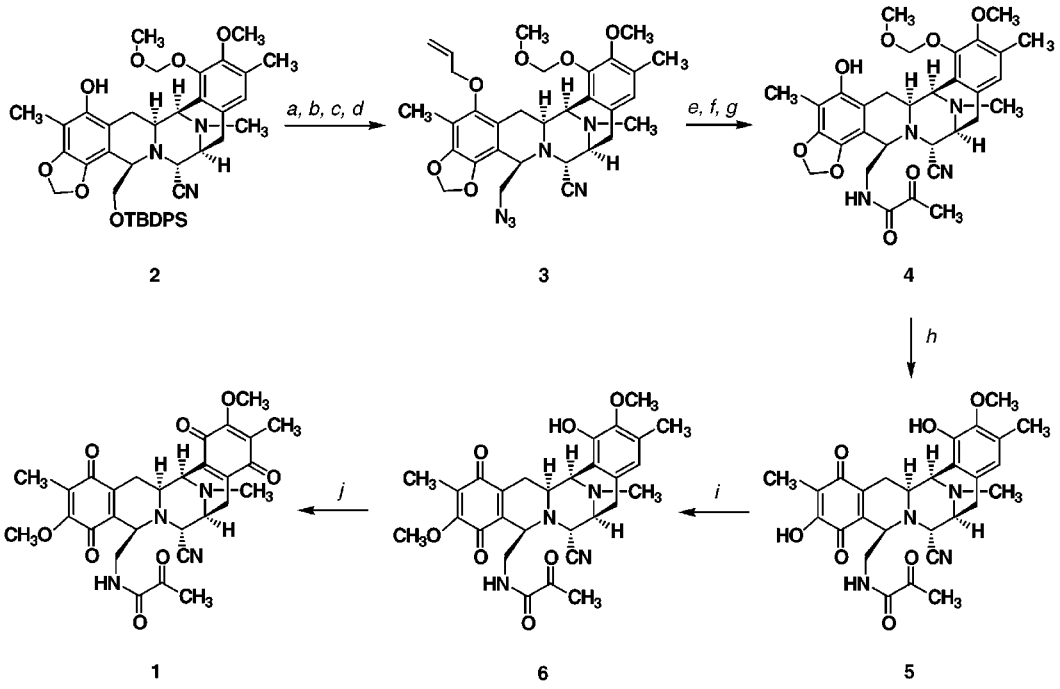
Saframycin A (1)

(1) (a) 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. (b) 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. (c) 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. (d) Wright, A. E.; Forleo, D. A.; Gunawardana, P. G.; Gunasekera, S. P.; Koehn, F. E.; McConnell, O. J. *J. Org. Chem.* **1990**, *55*, 4508. (e) Sakai, R.; Rinehart, K. L.; Guan, Y.; Wang, A. H.-J. *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 11456. (f) Sakai, R.; Jares-Erijman, E. A.; Manzanares, I.; Elipe, M. V. S.; Rinehart, K. L. *J. Am. Chem. Soc.* **1996**, *118*, 9017.

(2) Corey, E. J.; Gin, D. Y.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 9202.

10.1021/ol990553i CCC: $18.00
Published on Web 05/17/1999

Scheme 1. Synthesis of Saframycin A (**1**)



(a) Cs_2CO_3 (3.0 equiv), allyl bromide (4.0 equiv), DMF, 23 °C, 1.5 h, 85%. (b) TBAF (3.9 equiv), THF, 23 °C, 45 min, 99%. (c) TsOTs (3.5 equiv), *i*Pr_2NEt (2.0 equiv), DMAP (3.0 equiv), CH_2Cl_2, 23 °C, 13 hr, 69%. (d) LiN_3 (8.0 equiv), DMF, 70 °C, 20 min, 73%; (e) DTT (10.5 equiv), Et_3N (10.2 equiv), MeOH, 23 °C, 17 hr, 59%. (f) pyruvyl chloride (7.3 equiv), DMAP (4.9 equiv), CH_2Cl_2, 23 °C, 20 min, 87%. (g) $PdCl_2(PPh_3)_2$ (0.05 equiv), Bu_3SnH (2.7 equiv), AcOH (10.0 equiv), CH_2Cl_2, 23 °C, 10 min, 80%. (h) 1-fluoro-3,5-dichloropyridinium triflate (2.5 equiv), CH_2Cl_2, 0 °C, 2 h, 69%; (i) $TMSCHN_2$ (4.6 equiv), methanol-benzene (2:7), 23 °C, 20 min, 99%. (j) salcomine (0.16 equiv), O_2 (3 bar), THF, 23 °C, 26 h, 63%.

The pathway to saframycin A from the Et 743 intermediate **2** is outlined in Scheme 1. The phenolic function of **2** was protected as the allyl ether, and the *tert*-butyldiphenylsilyl group was cleaved with tetra-*n*-butylammonium fluoride to generate a primary alcohol which was converted via the corresponding tosylate (toluenesulfonic anhydride, diisopropylethylamine, and 4-(dimethylamino)pyridine) to the azide **3** by displacement using LiN_3 as nucleophile in dimethylformamide at 70 °C. The azide **3** was transformed into the phenolic pyruvamide **4** by the sequence (1) reduction of azide to primary amine with dithiothreitol and triethylamine in methanol at 23 °C,[5,6] (2) *N*-acylation with pyruvyl chloride and 4-(dimethylamino)pyridine in CH_2Cl_2, and (3) deallylation by treatment with tri-*n*-butyltin hydride and acetic acid in methylene chloride in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$. A novel oxidation was used to convert the phenol **4** to the corresponding 1,4-benzoquinone. Although 1-fluoro-3,5-dichloropyridinium triflate is generally used as a reagent for electrophilic fluorination,[7] it can serve also as an electron acceptor and as such effects the oxidation of phenol **4** to 1,4-benzoquinone and the concomitant cleavage of the methoxymethyl (MOM) protecting group to form **6** in a single step under mild conditions (CH_2Cl_2 solution at 0 °C for 2 h). One possible explanation of the facile MOM protecting group cleavage which is consistent with the isolation of phenol **5** rather than its further oxidation product(s) is the occurrence of the sequence:

$$\text{(a) } ROCH_2OCH_3 \rightarrow ROCHFOCH_3$$

$$\text{(b) } ROCHFOCH_3 + H_2O \rightarrow ROH + HCOOCH_3$$

Such a pathway implies that 1-fluoro-3,5-dichloropyridinium triflate might be a generally useful reagent for the selective cleavage of MOM ethers. This point is under investigation and will be reported separately.

(3) (a) Arai, T.; Takahashi, K.; Kubo, A. *J. Antibiot.* **1977**, *30*, 1015. (b) Arai, T.; Takahashi, K.; Nakahara, S.; Kubo, A. *Experientia* **1980**, *36*, 1025. For reviews on the saframycins, see: (a) Arai, T.; Kubo, A. In *The Alkaloids Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: New York, 1983; Vol. 21, Chapter 3. (b) Remers, W. A. In *The Chemistry of Antitumor Antibiotics*; Wiley: New York, 1988; Vol. 2, Chapter 3.

(4) (a) Fukuyama, T.; Yang, L.; Ajeck, K. L.; Sachleben, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 3712. (b) Myers, A. G.; Kung, D. *Book of Abstracts*, 216th National Meeting of the American Chemical Society, Boston, MA; American Chemical Society, Washington, DC, 1998; Abstract ORGN0501.

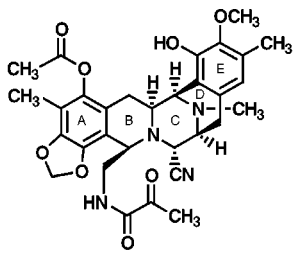
(5) (a) Staros, J. V.; Bayley, H.; Standring, D. N.; Knowles, J. R. *Biochem. Biophysic. Res. Commun.* **1978**, *80*, 568. (b) Bayley, H.; Standring, D. N.; Knowles, J. R. *Tetrahedron Lett.* **1978**, *39*, 3633.

(6) Hydrogen sulfide in pyridine was less effective for the azide → amine reduction, see: Adachi, T.; Yamada, Y.; Inoue, I. *Synthesis* **1977**, 45.

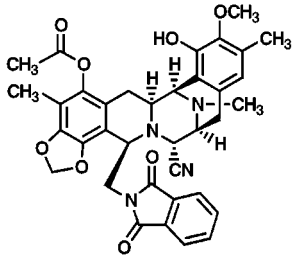
(7) (a) Umemoto, T.; Kawada, K.; Tomita, K. *Tetrahedron Lett.* **1986**, *27*, 4465. (b) Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563. (c) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737.

Selective *O*-methylation of **5** to form **6** was carried out using trimethylsilyldiazomethane (which was far more efficacious than diazomethane itself). Catalytic oxidation of **6** in a THF solution using dioxygen and a catalytic amount of cobalt bis-salicylidineethylenediamine complex (salcomine) provided saframycin A (**1**) cleanly.[8]

The A-ring monoquinone **6** can be regarded as a pentacyclic hybrid of ecteinascidin and saframycin structures. In connection with the correlation of antitumor activity of saframycin and ecteinascidin type compounds with this structure, we decided to evaluate compound **6** and also the alternative Et 743−saframycin hybrid **7**, which has the



7



Phthalascidin

characteristic saframycin A appendage on ring B but is nonquinoid at rings A and E. This compound was readily prepared from phenol **4** in 64% overall yield by acetylation (Ac_2O, DMAP in CH_2Cl_2 at 23 °C) and MOM ether cleavage (4:1:1 $CF_3CO_2H-H_2O-$THF at 23 °C for 11 h).

(8) De Jonge, C. R. H. I.; Hageman, H. J.; Hoentjen, G.; Mus, W. J. *Organic Syntheses;* Wiley: New York, 1988; Collect Vol. VI, p 412.

(9) Martinez, E. J.; Owa, T.; Schreiber, S. L.; Corey, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 3496.

The antitumor activities of **1**, **6**, **7**, Et 743, and phthalascidin (Pt 650, the most active of a series of synthetic Et 743 analogues)[9] were determined using four human cancer cell lines with the results shown in Table 1. A number of

Table 1. Antiproliferative Activities of Et 743, Saframycin A, and Analogues (IC_{50} (nM))

compd	A-549 (lung)	HCT 116 (colon)	A 375 (melanoma)	PC-3 (prostate)
7	16	3.4	1.2	3.6
6	>180	47	26	44
1	430	39	30	27
Et 743	1.0	0.50	0.15	0.70
Pt 650	0.95	0.38	0.17	0.55

important points emerge from these data. It is clear that saframycin A is at least 2 orders of magnitude less active than ecteinascidin 743 or phthalascidin. Comparison of the A-ring monoquinone **6** and the analogous nonquinone structure **7** reveals that a quinoid A-ring lowers potency relative to the benzenoid A-ring counterpart by about 10-fold. These results underscore the importance of the benzenoid A-ring to the superior antitumor activity of Et 743 and Pt 650.

Acknowledgment. This work was assisted by a grant from the National Institutes of Health and a graduate student fellowship from Schering Plough.

OL990553I