Tetrahedron Letters 51 (2010) 6498–6499

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A new method for the synthesis of the marine alkaloid fascaplysin

Maxim E. Zhidkov *, Olga V. Baranova, Natalya S. Kravchenko, Sergey V. Dubovitskii

Department of Chemistry, Far Eastern National University, 8 Sukhanov Str., Vladivostok 690950, Russia

ARTICLE INFO

Article history:
Received 13 August 2010
Revised 15 September 2010
Accepted 24 September 2010
Available online 8 October 2010

Keywords:
Synthesis
Homofascaplysin C
Fascaplysin
Pyrido[1,2-*a*:3,4-*b*′]diindole

ABSTRACT

A new method for the synthesis of the marine alkaloid fascaplysin has been developed via a simple and practical approach to pyrido[1,2-*a*:3,4-*b*′]diindole ring system formation. Conversion of the marine alkaloid homofascaplysin C into fascaplysin is also described.

The pentacyclic pyrido[1,2-*a*:3,4-*b*′]diindole system (**1**) forms the basis of a number of marine alkaloids, including the well known red pigment fascaplysin (**2**) from the marine sponge *Fascaplysinopsis Bergquist* sp. (Fig. 1).[1] This compound has a broad range of biological activity,[2] and in particular, it demonstrates the selective inhibition of cyclin-dependent kinase 4, which regulates the G_0–G_1/S checkpoint of the cell cycle.[3] Owing to this fact, fascaplysin can be used as a lead compound for creating novel anticancer drugs. Several methods to prepare fascaplysin have been described in the literature.[4] We report herein two variations on the synthesis of fascaplysin based on a common approach, which we previously elaborated for heterocyclic system **1**.[5] One of variants includes an efficient one-step conversion of the marine alkaloid homofascaplysin C (**3**) into fascaplysin.

Earlier we reported a simple and efficient synthesis of the marine alkaloid homofascaplysin C.[5] This method was based on formation of the pyrido[1,2-*a*:3,4-*b*′]diindole system by in situ Fischer cyclization between indoloketone **4a** and phenylhydrazine (Scheme 1).[6] Intermediate **5a** was converted into target compound **3** in one step using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) as the oxidizing agent.

To obtain fascaplysin via this strategy we started with unsubstituted indoloketone **4b**, the synthesis of which was described in the literature.[7] Our attempts to obtain the product of Fischer cyclization without isolation of the corresponding phenylhydrazone **6** failed under various conditions, however, the isolation of the intermediate phenylhydrazone **6** did not cause any difficulties. In the next stage, most standard conditions were ineffective because

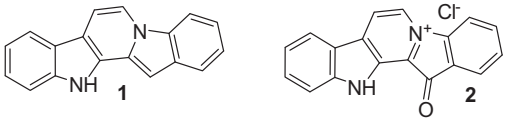


Figure 1. Structures of pyrido[1,2-*a*:3,4-*b*′]diindole (**1**) and its natural representative fascaplysin (**2**).

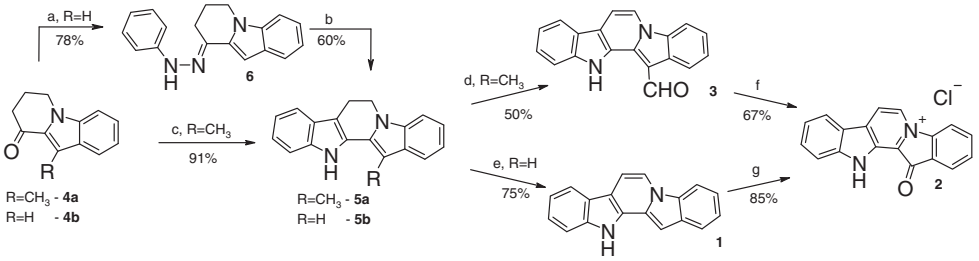
the rearrangement was either incomplete or was accompanied by resinification of the reaction mixture. We were able to synthesize compound **5b** using *p*-toluenesulfonic acid in benzene, in 60% yield.[8] Dehydrogenation of compound **5b** was performed over Pd/C in preparative yield. The main spectral characteristics of the obtained product were identical to those of compound **1** presented in the literature.[4a] Oxidation of compound **1** to fascaplysin was also described in that article.[4a] Thus, fascaplysin can be synthesized in seven steps from commercially available ethyl indole-2-carboxylate in 17% overall yield.

To minimize the losses in the conversion of **4b** into **5b** we decided to employ a one-step process to convert **4a** into **5a** via removal of the methyl by oxidation to a carboxyl group and decarboxylation. Thus we could realize the conversion of homofascaplysin C (**3**) into fascaplysin in one step through Baeyer–Villiger rearrangement under the action of *meta*-chloroperoxybenzoic acid (*m*-CPBA).[9]

In the second variant of our method fascaplysin was obtained in five steps starting from readily available 3-methylindole in 18% overall yield. This new method for the synthesis of fascaplysin should enable the preparation of a wide range of fascaplysin derivatives from readily available phenylhydrazines and opens up fresh opportunities for detailed SAR studies of these potentially bioactive compounds.

* Corresponding author. Tel.: +7 4232 429 510; fax: +7 4232 429 510.
E-mail address: mzhidkov@rambler.ru (M.E. Zhidkov).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.09.120



Scheme 1. Reagents and conditions: (a) Ph–NH–NH_2·HCl, EtOH, rt, 2 h; (b) TsOH, PhH, Δ, 20 min; (c) Ph–NH–NH_2·HCl, AcOH, Δ, 4 h; (d) DDQ, 1,4-dioxane, Δ, 2 h; (e) Pd/C, $(EtOCH_2CH_2)_2$, Δ, 6 h; (f) *m*-CPBA, EtOAc, rt, 24 h; (g) CH_3CO_3H, MeOH, 0 °C, 45 min (Ref. 4a).

Acknowledgements

The research described in this publication was made possible in part by Grants from the Russian Ministry of Education and Science Nos. P745 and 02.552.11.7043 and the award No. RUXO-003-VL-06 from the CRDF.

References and notes

1. Roll, D. M.; Ireland, C. M.; Lu, H. S.; Clardy, J. *J. Org. Chem.* **1988**, *53*, 3276–3278.
2. For example, see: (a) Jimenez, C.; Quinoa, E.; Adamczeski, M.; Hunter, L. M.; Crews, P. *J. Org. Chem.* **1991**, *56*, 3403–3410; (b) Schmidt, E. W.; Faulkner, D. J. *Tetrahedron Lett.* **1996**, *37*, 3951–3954; (c) Kirsch, G.; Konig, G. M.; Wright, A. D.; Kaminsky, R. *J. Nat. Prod.* **2000**, *63*, 825–829; (d) Charan, R. D.; McKee, T. C.; Gustafson, K. R.; Pannell, L. K.; Boyd, M. R. *Tetrahedron Lett.* **2002**, *43*, 5201–5204; (e) Popov, A. M.; Stonik, V. A. *Antibiot. Khimioter.* **1991**, *36*, 12–14; (f) Hormann, A.; Chaudhuri, B.; Fretz, H. *Bioorg. Med. Chem.* **2001**, *9*, 917–921.
3. Soni, R.; Muller, L.; Furet, P.; Schoepfer, J.; Stephan, C.; Zunstein-Mecker, S.; Fretz, H.; Chaudhuri, B. *Biochem. Biophys. Res. Commun.* **2000**, *275*, 877–884.
4. (a) Gribble, G. W.; Pelcman, B. *J. Org. Chem.* **1992**, *57*, 3636–3642; (b) Rocca, P.; Marsais, F.; Godart, A.; Quéguiner, G. *Tetrahedron Lett.* **1993**, *34*, 7917–7918; (c) Molina, P.; Fresneda, M.; Garciazafra, S.; Almendros, P. *Tetrahedron Lett.* **1994**, *35*, 8851–8854; (d) Radchenko, O. S.; Novikov, V. L.; Elyakov, G. B. *Tetrahedron Lett.* **1997**, *38*, 5339–5342.
5. Dubovitskii, S. V. *Tetrahedron Lett.* **1997**, *37*, 5207–5208.
6. Jirkovsky, I.; Sontroch, G.; Bandy, R.; Oshiro, G. *J. Med. Chem.* **1987**, *30*, 388–394.
7. Bit, R. A.; Davis, P. D.; Hill, C. H.; Keech, E.; Vesey, D. R. *Tetrahedron* **1991**, *47*, 4645–4664.
8. 6,7-Dihydro-12*H*-pyrido[1,2-*a*:3,4-*b*′]diindole (**5b**). Phenylhydrazone **6** (500 mg, 1.8 mmol) was added to a solution of TsOH·H_2O (1.0 g, 5.4 mmol) in 8 mL of dry benzene. The reaction mixture was refluxed for 30 min, then cooled and diluted with benzene (20 mL), washed with aq. $NaHCO_3$ (3 × 30 mL), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure. The crude product, after recrystallization from hexane/toluene, gave **5b** (278 mg, 60%). The main spectral characteristics of **5b** were identical to those described in the literature.[4a] These conditions for Fischer rearrangement were first proposed in the publication: Murakami, Y.; Yokoyama, Y.; Miura, T.; Hirasawa, H.; Kamimura, Y.; Izaki, M. *Heterocycles* **1984**, *22*, 1211–1215.
9. Conversion of homofascaplysin C (**3**) into fascaplysin (**2**). A mixture of homofascaplysin C (71 mg, 0.25 mmol) and *m*-CPBA (130 mg, 0.75 mmol) in EtOAc (4 mL) was stirred at room temperature for 24 h. The reaction mixture was washed with H_2O (3 × 10 mL) and acidified with hydrochloric acid. The combined aqueous layer was extracted with EtOAc (3 × 3 mL) and then evaporated under reduced pressure to give **2** as a red powder (52 mg, 67%); the main spectral characteristics of which were identical to those of fascaplysin.