Tetrahedron 68 (2012) 7280–7287

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

# Total synthesis of infectopyrone, aplysiopsenes A–C, *ent*-aplysiopsene D, phomapyrones A and D, 8,9-dehydroxylarone, and nectriapyrone

Oliver Geiseler, Joachim Podlech *

*Institut für Organische Chemie, Karlsruher Institut für Technologie (KIT), Fritz-Haber-Weg 6, 76131 Karlsruhe, Germany*

ARTICLE INFO

*Article history:*
Received 6 June 2012
Accepted 28 June 2012
Available online 4 July 2012

*Keywords:*
Polyketides
Fungal metabolites
Olefination
2-Pyrones
Total synthesis

ABSTRACT

The total synthesis of the 2-pyrone natural products nectriapyrone, aplysiopsenes A–C, *ent*-aplysiopsene D, phomapyrones A and D, and of 8,9-dehydroxylarone were achieved by Wittig olefination starting with vermopyrone. Infectopyrone was synthesized by Horner–Wadsworth–Emmons reaction starting with phomapyrone D. Racemic phomapyrone C methyl ether was obtained by hydrogenation of nectriapyrone. The total syntheses were achieved starting from commercially available 3,5-heptanedione and led to the desired natural products in 18–46% over 5–6 steps, whereupon all five-step syntheses were carried out with a single chromatographic workup. The total synthesis of infectopyrone, aplysiopsenes A–D, of phomapyrones A and D, and of 8,9-dehydroxylarone were achieved for the first time, giving unambiguous proof for the proposed structures of these natural products.



## 1. Introduction

2-Pyrones, a class of natural products with a vast variety of structures, are present in bacteria, microbials, plants, insects, and animal systems. They show a plethora of different biological activities.[1] Among the 2-pyrones are prominent representatives like the coumarins, e.g., the anticoagulants warfarin[2] and dicoumarol. The extremely toxic and carcinogenic aflatoxins also have a 2-pyrone substructure.[3] They are produced by *Aspergillus* ssp. growing on food and feed and thus are mycotoxins.[4] Infectopyrone (**1**), a 2-pyrone first isolated from *Alternaria infectoria* is furthermore produced by *Stemphyllium* and *Ulocladium* sp. (Fig. 1). It shows cytotoxicity against mouse P388 leukemia cells ($ID_{50}$ >25 μg/mL).[5] Vermopyrone (**2**) and nectriapyrone (**3**) are truncated derivatives of infectopyrone,[6] where nectriapyrone is antibiotic against *Staphylococcus aureus* at a 30 ppm level.[7] The biosynthesis of nectriapyrone and vermopyrone was investigated by Avent et al. giving proof for the polyketide character of the 2-pyrones although they were supposed to be monoterpens. $^{13}C$-labeled sodium acetate, methionine and acetic acid were separately fed to *Gliocladium vermoesenii* disproving the terpenoid origin of nectriapyrone and vermopyrone.[8]

The structurally closely related aplysiopsenes A–D (**4**–**7**) were first isolated from the hermaeidan sacoglossan *Aplysiopsis formosa*. It is supposed that they are part of the chemical defense of the mollusks and are involved in the recovery of detached extremities. They are polyketides produced via a mixed acetate/propionate pathway.[9] Aplysiopsene D (**7**) was also isolated from the sea fan-derived fungus *Nigrospora* sp. PSU-F12[10] and aplysiopsene C (**6**) was isolated from *Xylaria hypoxylon* (here named as xylarone).[11] Hardly anything is known about biological activities of these compounds, but aplysiopsene C is cytotoxic—it reduces cell proliferation by 50% ($IC_{50}$) between 40 μg/mL (Colo-320 cells) and 50 μg/mL (L1210 cells), where 8,9-dehydroxylarone (**8**) was slightly more active (25–50 μg/mL).[11] Phomapyrone A (**9**, phomenin A) was isolated (together with phomenin B) for the first time from *Phoma tracheiphila* in 1993[12] and in 2009 from *A. infectoria*.[13] Phomapyrones A–G (**9**–**15**) were isolated from *Leptosphaeria maculans*, the anamorphous stage of *Phoma lingams*,[14] phomapyrones B (**10**) and C (**11**) were isolated from *Paecilomyces lilacinus*,[15] and phomapyrones A (**9**), D (**12**) and G (**15**) were isolated together with infectopyrone from *Alternaria brassicicola* in 2009.[16] Phomapyrone A showed activity ($LD_{50}$: 38.9 μg/mL) in a brine shrimp bioassay indicating cytotoxicity and insecticidal activity[12] and phomapyrones A–C are phytotoxic.[14] Vermopyrone, nectriapyrone and various not yet named pyrones, e.g., (6-(1,2-dimethyloxiran-1-yl)-4-methoxy-3-methyl-2*H*-pyran-2-one) were isolated from *Cephalotaxus hainanensis*. This fungus is notorious to Chinese medicine for its anticancer activity, but detailed biological studies have not yet been reported for these recently isolated pyrones.[17] Where total syntheses of nectriapyrone[18] and of gymnoconjugatins A and B[19] have been published, no total syntheses of aplysiopsenes, of phomapyrones and most of the related 2-pyrones have been reported. As a part of our ongoing activities in the synthesis of mycotoxins from *Alternaria* ssp.,[20] we developed total syntheses of infectopyrone, aplysiopsenes A–D, of phomapyrones A, C, and D, of 8,9-dehydroxylarone and of nectriapyrone, which are given in this paper.

* Corresponding author. Tel.: +49 721 608 43209; fax: +49 721 608 47652; e-mail addresses: joachim.podlech@kit.edu, joachim.podlech@ioc.uka.de (J. Podlech).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.06.104

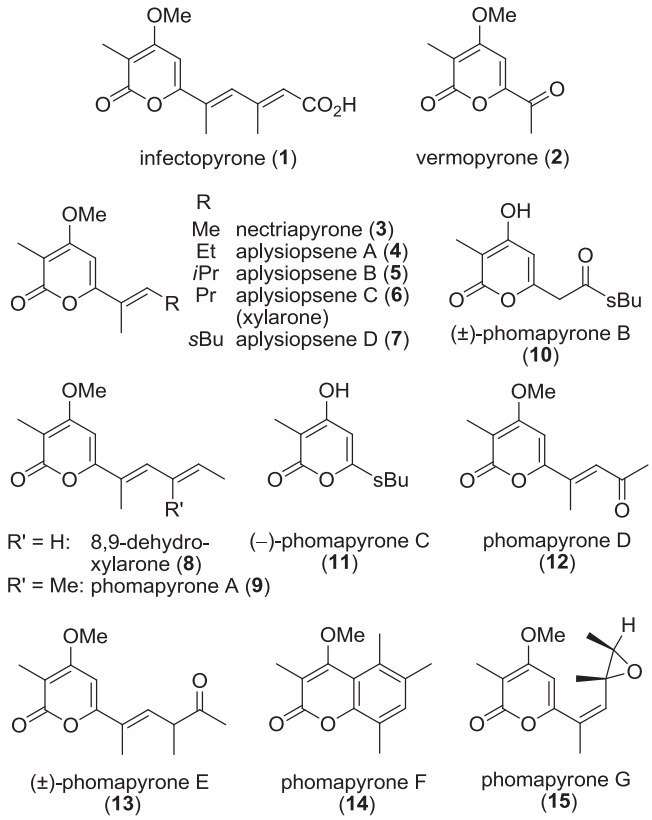
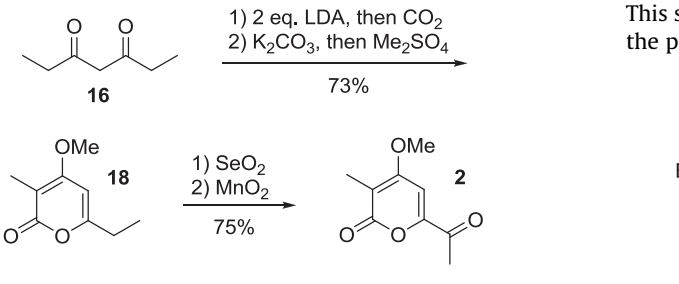



**Fig. 1.** α-Pyrone-derived natural products.

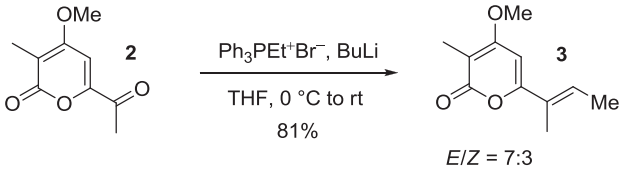
## 2. Total synthesis of nectriapyrone and aplysiopsenes

We considered vermopyrone (**2**) a suitable starting material for the aplysiopsenes following a Wittig olefination strategy. Vermopyrone (**2**) had been synthesized by Coleman et al.[19] in four steps starting with 3,5-heptanedione (**16**); we used their protocol with minor modifications (Scheme 1). After formation of the pyrone scaffold **18**,[21] we oxidized the allylic position using selenium dioxide[19] followed by an oxidation with manganese dioxide to furnish vermopyrone (**2**) with 55% yield over four steps. Utilizing manganese dioxide, activated according to a method by Attenburrow,[22] led to the given, somewhat better yield and—more important—to essentially pure vermopyrone (**2**), making special purification protocols obsolete and thus significantly facilitating the next steps of the total syntheses. Oxidation of the intermediate allylic alcohol could also be achieved with Dess–Martin periodinane or using a mixture of commercially available manganese dioxide and potassium permanganate,[23] albeit with lower yields.

In contrast to Coleman's work, where a Takai olefination followed by a Stille coupling was employed,[19] we chose a Wittig olefination to assemble the olefinic natural products. Using this route, we could avoid hazardous organostannanes and—not essentially a drawback—we additionally gained access to *Z*-configured products, which could be similarly tested on their biological activities. For a proof of principle, we started with the synthesis of nectriapyrone (**3**), a pyrone first synthesized in 1976 by Boll et al. in 6% over four steps.[18] Vermopyrone (**2**) was reacted with an ylide prepared from the respective ethylphosphonium salt to yield nectriapyrone (**3**) with an *E*/*Z* selectivity of 7:3, where the natural *E* isomer was obtained by a simple chromatography (Scheme 2). It was obtained with an improved 44% yield (over five steps) and was unambiguously identified by comparison of published analytical data.



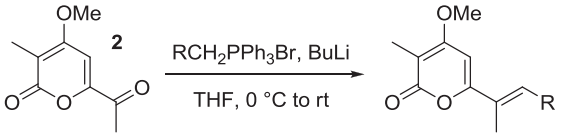

**Scheme 1.** Synthesis of vermopyrone (**2**).




**Scheme 2.** Synthesis of nectriapyrone (**3**).

Aplysiopsenes were obtained by analogous olefination protocols. Reaction of vermopyrone (**2**) with the respective phosphorous ylides (prepared from the phosphonium bromides with butyl lithium) gave rise to the corresponding aplysiopsenes with 33–80% yield as mixtures of diastereoisomers (Table 1). Chromatography furnished the *E*-configured natural aplysiopsenes A–C with 18–56% yield and thus with total yields of 10–31% over five steps. While the precursor vermopyrone was stable at rt at least for several weeks, the aplysiopsenes turned out to be quite unstable. NMR samples showed signals of decomposition products when stored for one week at 4 °C.

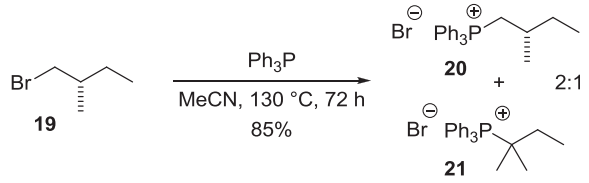
**Table 1**
Wittig reactions toward 2-pyrone-derived natural products




| Product | R | Yield [%] | *E*/*Z* | Yield *E* [%] |
|---|---|---|---|---|
| Nectriapyrone (**3**) | Me | 81 | 7:3 | 57 |
| Aplysiopsene A (**4**) | Et | 76 | 7:3 | 53 |
| Aplysiopsene B (**5**) | $^{i}$Pr | 44 | 4:6 | 18 |
| Aplysiopsene C (**6**) | Pr | 80 | 7:3 | 56 |
| (*ent*)-Aplysiopsene D (**7**) | $^{s}$Bu | 33 | 1:1 | 17 |
| Phomapyrone A (**9**) | (*E*)-But-2-en-2-yl | 78 | 9:11 | 35 |
| Phomapyrone D[a] (**12**) | Ac | 84 | 7:3 | 59 |
| 8,9-Dehydroxylarone (**8**) | (*E*)-Propen-1-yl | 70 | 7:3 | 49 |

[a] Differing reaction conditions. See Experimental section.

Synthesis of enantiomerically pure (*S*)-2-methylbut-1-yltriphenylphosphonium bromide (**20**), the Wittig precursor for the olefination toward aplysiopsene D (**7**), turned out to be not straightforward. The standard protocol[24a] for the reaction of the bromide **19** with triphenylphosphine yielded the phosphonium salt **20** together with a rearranged product **21** in a 2:1 ratio (Scheme 3). This side product was not mentioned in the published synthesis of the phosphonium salt **20**.[24]




**Scheme 3.** Side reaction in the formation of phosphonium salt **20**.