ORGANIC LETTERS

2013
Vol. 15, No. 8
2006–2009

Synthesis of the Griseusin B Framework via a One-Pot Annulation–Methylation–Double Deprotection–Spirocyclization Sequence

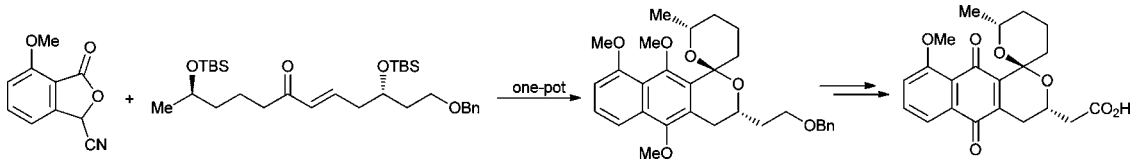
Briar J. Naysmith and Margaret A. Brimble*

School of Chemical Sciences, The University of Auckland, 23 Symonds Street, Auckland, New Zealand

m.brimble@auckland.ac.nz

Received March 14, 2013

ABSTRACT



A highly convergent synthesis of the griseusin B scaffold is described. The key step involves an efficient one-pot Hauser–Kraus annulation–methylation–double deprotection–spirocyclization sequence that directly affords the target parent tetracyclic ring system.

The griseusins are a subgroup of the pyranonaphthoquinone family of natural products[1] that contain a 6,6-spiroketal ring fused to a juglone moiety. The first in the family to be isolated were griseusins A **1** and B **2** from a *Streptomyces griseus* K-63 bacterium found in a soil sample in 1976 (Figure 1).[2] **1** contains a closed γ-lactone ring whereas in **2** the lactone is opened to the carboxylic acid. Since then, 15 more griseusin natural products (**3**–**17**) (Figure 1)[3] have been isolated that differ in oxygenation patterns and stereochemistry around the spiroketal ring, with variable substitution at C-9 of the dihydropyran ring and the C2a–C8a quinone double bond. 3′-*O*-α-D-Forosaminyl-(+)-griseusin A **8** possesses an additional sugar moiety[3a] while yoropyrazone **14** contains a novel amide side chain and a fused 2-pyridazone ring.[3g] The griseusins demonstrate a variety of antibacterial and anticancer properties.[2,3] Pyranonaphthoquinones in general have been proposed to act as bioreductive alkylating agents[4] and also exhibit selective inhibitory activity against serine/threonine AKT,[5] both of which may contribute to their mechanism of action against cancer cells. This attractive biological profile, combined with their intricate structures, makes the griseusins and their analogues appealing synthetic targets. Our group is interested in the synthesis of analogues of the griseusins and other pyranonaphthoquinones for biological evaluation as part of an ongoing medicinal chemistry program.[6] To date, there has only

(1) For an extensive review on pyranonaphthoquinones, see: Sperry, J.; Bachu, P.; Brimble, M. A. *Nat. Prod. Rep.* **2008**, *25*, 376.

(2) Tsuji, N.; Kobayashi, M.; Wakisaka, Y.; Kawamura, Y.; Mayama, M.; Matsumoto, K. *J. Antibiot.* **1976**, *29*, 7.

(3) (a) Maruyama, M.; Nishida, C.; Takahashi, Y.; Naganawa, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1994**, *47*, 952. (b) Igarashi, M.; Chien, W.; Tsuchida, T.; Umekita, M.; Sawa, T.; Naganawa, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1995**, *48*, 1502. (c) Li, X.; Zheng, Y.; Sattler, I.; Lin, W. *Arch. Pharmacal Res.* **2006**, *29*, 942. (d) Li, Y.-Q.; Li, M.-G.; Li, W.; Zhao, J.-Y.; Ding, Z.-G.; Cui, X.-L.; Wen, M.-L. *J. Antibiot.* **2007**, *60*, 757. (e) He, J.; Roemer, E.; Lange, C.; Huang, X.; Maier, A.; Kelter, G.; Jiang, Y.; Xu, L.-H.; Menzel, K.-D.; Grabley, S.; Fiebig, H.-H.; Jiang, C.-L.; Sattler, I. *J. Med. Chem.* **2007**, *50*, 5168. (f) Abdelfattah, M. S.; Kazufumi, T.; Ishibashi, M. *J. Antibiot.* **2011**, *64*, 729. (g) Abdelfattah, M. S.; Toume, K.; Ishibashi, M. *J. Antibiot.* **2012**, *65*, 245. (h) Ding, Z.-G.; Zhao, J.-Y.; Li, M.-G.; Huang, R.; Li, Q.-M.; Cui, X.-L.; Zhu, H.-J.; Wen, M.-L. *J. Nat. Prod.* **2012**, *75*, 1994.

(4) Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249.

(5) Salaski, E. J.; Krishnamurthy, G.; Ding, W.-D.; Yu, K.; Insaf, S. S.; Eid, C.; Shim, J.; Levin, J. I.; Tabei, K.; Toral-Barza, L.; Zhang, W.-G.; McDonald, L. A.; Honores, E.; Hanna, C.; Yamashita, A.; Johnson, B.; Li, Z.; Laakso, L.; Powell, D.; Mansour, T. S. *J. Med. Chem.* **2009**, *52*, 2181.

(6) (a) Sperry, J.; Lorenzo-Castrillejo, I.; Brimble, M. A.; Machin, F. *Bioorg. Med. Chem.* **2009**, *17*, 7131. (b) Hume, P. A.; Sperry, J.; Brimble, M. A. *Org. Biomol. Chem.* **2011**, *9*, 5423. (c) Bridewell, D. J. A.; Sperry, J.; Smith, J. R.; Kosim-Satyaputra, P.; Ching, L.-M.; Jamie, J. F.; Brimble, M. A. *Aust. J. Chem.* **2013**, *66*, 40.

(7) Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Org. Chem.* **1983**, *48*, 2311.

10.1021/ol400686f
Published on Web 04/05/2013

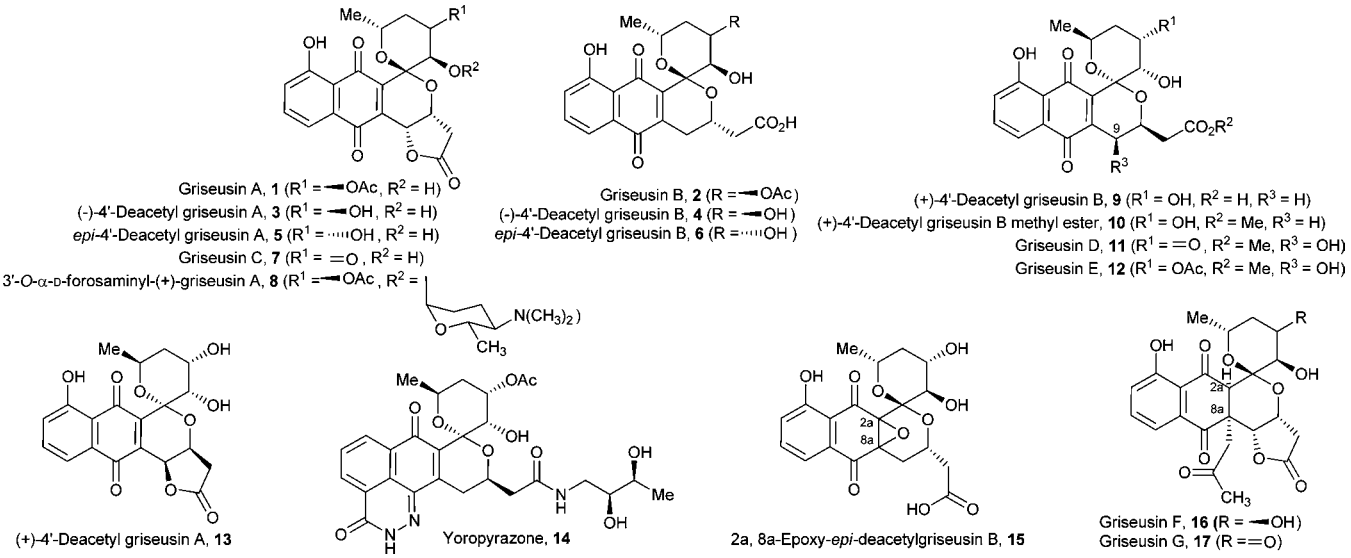


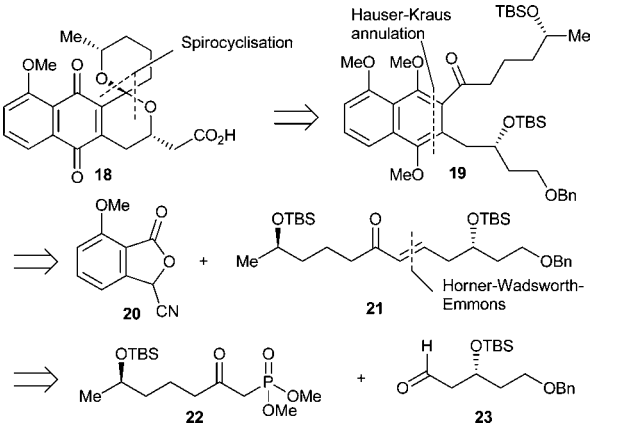
Figure 1. Structures of the griseusin family of natural products.

been one total synthesis of griseusins A **1** and B **2**[7] although a number of syntheses of griseusin analogues have been published.[8]

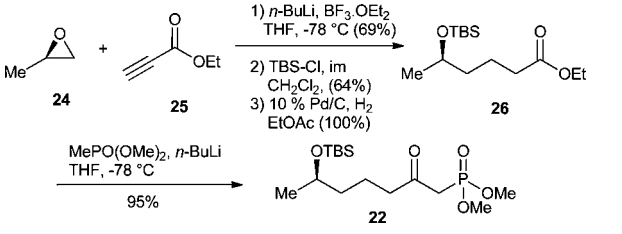
Based on previous syntheses of simpler pyranonaphthoquinones,[9] we focused the current research on construction of the pyranonaphthoquinone framework of griseusin B **2** using a Hauser–Kraus (HK) annulation strategy in order to develop a highly convergent synthetic route that could be easily adapted to the synthesis of the natural products and other analogues. We herein report the synthesis of the griseusin B analogue **18**. Our retrosynthetic analysis of **18** relied on deprotection and spirocyclization of an advanced precursor **19**, itself available from HK annulation between stabilized phthalide **20** and chiral enone **21** (Scheme 1). Enone **21** can in turn be accessed via a Horner–Wadsworth–Emmons (HWE) reaction between saturated phosphonate **22** and aldehyde **23**.

Thus, our synthesis began with the preparation of the phosphonate coupling partner **22** (Scheme 2). (*R*)-Propylene oxide **24** was opened with the anion of commercially available ethyl propiolate **25**[10] followed by TBS protection of the newly formed secondary alcohol and subsequent hydrogenation under standard conditions to give ester **26**. Addition of lithiated dimethyl methylphosphonate[11] afforded the α-keto phosphonate **22** in good yield over four steps.

Scheme 1. Retrosynthesis of Griseusin B Analogue, **18**



Scheme 2. Synthesis of Phosphonate, **22**



(8) (a) Masamoto, K.; Takeuchi, Y.; Takeda, K.; Yoshii, E. *Heterocycles* **1981**, *16*, 1659. (b) Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Org. Chem.* **1982**, *47*, 4725. (c) Brimble, M. A.; Nairn, M. R. *J. Chem. Soc., Perkin Trans. 1* **1990**, 169. (d) Brimble, M. A.; Nairn, M. R. *J. Chem. Soc., Perkin Trans. 1* **1992**, 579. (e) Brimble, M. A.; Nairn, M. R. *Molecules* **1996**, *1*, 3. (f) Brimble, M. A.; Nairn, M. R.; Park, J. *Org. Lett.* **1999**, *1*, 1459. (g) Brimble, M. A.; Nairn, M. R.; Park, J. S. O. *J. Chem. Soc., Perkin Trans. 1* **2000**, 697.

(9) (a) Gibson, J. S.; Andrey, O.; Brimble, M. A. *Synthesis* **2007**, 2611. (b) Andrey, O.; Sperry, J.; Larsen, U. S.; Brimble, M. A. *Tetrahedron* **2008**, *64*, 3912. (c) Brimble, M. A.; Gibson, J. S.; Sejberg, J. J. P.; Sperry, J. *Synlett* **2008**, 867. (d) Sperry, J.; Gibson, J. S.; Sejberg, J. J. P.; Brimble, M. A. *Org. Biomol. Chem.* **2008**, *6*, 4261.

(10) Tan, N. P. H.; Donner, C. D. *Tetrahedron* **2009**, *65*, 4007.

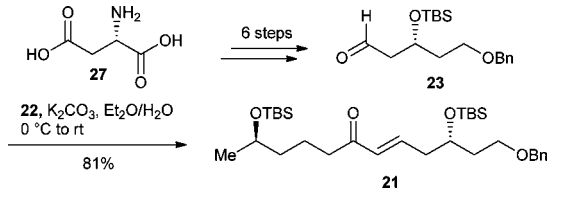
(11) McLeod, M. C.; Wilson, Z. E.; Brimble, M. A. *J. Org. Chem.* **2012**, *77*, 400.

(12) (a) Robinson, J. E.; Brimble, M. A. *Org. Biomol. Chem.* **2007**, *5*, 2572. (b) Matsuura, F.; Peters, R.; Anada, M.; Harried, S. S.; Hao, J.; Kishi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 7463.

(13) Uenishi, J. I.; Ohmi, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2756.

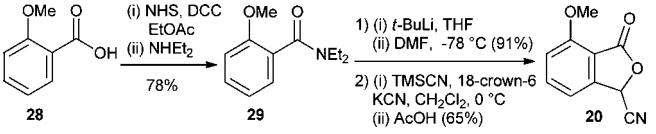
The aldehyde coupling partner **23** was synthesized in six steps according to literature methods,[12] using the chiral pool material L-aspartic acid **27** as the source of the β-hydroxy chiral center (Scheme 3). HWE reaction of aldehyde **23** with phosphonate **22** using mild biphasic conditions[13] proceeded smoothly forming the highly substituted *E*-enone **21** required for the key annulation step.

Scheme 3. Synthesis of Enone, **21**



Synthesis of the cyanophthalide coupling partner **20** for the HK annulation was carried out from commercially available *o*-anisic acid **28** (Scheme 4). **28** was converted to the corresponding amide **29** using a mild procedure involving activation as the *N*-hydroxysuccinimide (NHS) ester followed by substitution with diethylamine in one pot.[14] Phthalide **20** was generated over two additional steps from amide **29** using literature procedures.[9c,15]

Scheme 4. Synthesis of Cyanophthalide, **20**



Attention was next turned to the key HK annulation reaction of phthalide **20** with enone **21**, first attempted using procedures that had previously proven successful in our group (Scheme 5).[16] HK annulations are known to form a mixture of quinone and hydroquinone products. Therefore, it was our intention to effect the annulation using *t*-BuOK as the base followed by trapping the hydroquinone as a dimethyl ether. This can be achieved by fully reducing the quinone to the hydroquinone using $Na_2S_2O_4$ under hydrogen followed by the addition of base and Me_2SO_4.[16] Accordingly, the annulation was carried out with *t*-BuOK in DMSO until TLC indicated complete consumption of enone **21**. The crude annulation mixture was then subjected to reductive methylation conditions overnight (Table 1, entry 1). Extraordinarily, the sole product isolated was not the expected methylated hydroquinone **19**, but the double TBS-deprotected and spirocyclized product **32** (Scheme 5). It is remarkable that these seven transformations

(14) Cline, G. W.; Hanna, S. B. *J. Am. Chem. Soc.* **1987**, *109*, 3087.
(15) de Silva, S. O.; Reed, J. N.; Snieckus, V. *Tetrahedron Lett.* **1978**, *19*, 5099.
(16) Rathwell, K.; Sperry, J.; Brimble, M. A. *Tetrahedron* **2010**, *66*, 4002.

Scheme 5. Synthesis of Spiroketal, **32**

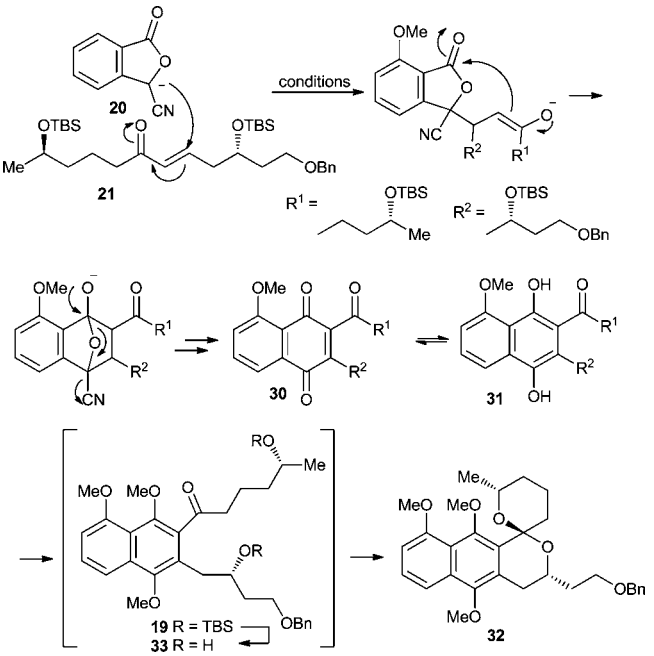


Table 1. HK Annulation of Enone, **21** (1 equiv), and Phthalide, **20**

	annulation conditions[a]		methylation conditions[a]		
entry	**20**	*t*-BuOK	NaOH	Me_2SO_4	yield **32**
	two step process[b]				
1	1.1	1.2	20	30	10%
2	1.2	1.3	30	45	15%
3	1.4	1.5	30	40	18%
	one-pot process[c]				
4	1.9	1.5	30	40	32%
5	2.2	2.0	30	40	49%

[a] Equivalents relative to **21**. [b] Annulation in DMSO, reduction/methylation in THF (see Supporting Information). [c] Annulation/methylation in one pot in THF.

take place in a simple reaction sequence. The anion of phthalide **20** undergoes Michael addition to enone **21** followed by Dieckmann-like condensation and oxidation to form the bicyclic system. Equilibrium between the quinone **30** and hydroquinone **31** products is pushed toward **31** by reduction and trapping as the dimethoxyhydroquinone **19**. Double TBS deprotection forms the dihydroxyketone **33**, followed by spirocyclization to give the isolated spiroketal product **32**. Intermediate **19** could be observed by TLC and isolated in small amounts, suggesting that methylation occurs prior to TBS deprotection and spirocyclization. An increase in yield from 10% to 18% was achieved by adding more phthalide **20** and base to the annulation reaction, as well as additional base and Me_2SO_4 in the methylation step (Table 1, entries 3–4).

Next, an attempt was made to effect the transformation in one pot as well as remove the $Na_2S_2O_4$ reduction step prior to methylation, as no change by TLC was observed after reduction. Gratifyingly, the one-pot annulation–methylation–double deprotection–spirocyclization procedure afforded the desired spiroketal **32** in improved yield (32%) (Table 1, entry 4). The addition of more phthalide **20** and base in the annulation step further increased the yield to 49% (Table 1, entry 5). This efficient reaction sequence delivers a single isomer of a complex hetereocyclic product from two relatively simple starting materials in one pot in reasonable yield.

Computer modeling[17] of the two spiroketal anomers of **32** predicts that the isomer with the C2′–O1′ bond pseudoaxial is significantly lower in energy. In a parallel study, a crystal structure of 10-*epi*-**32** was obtained which confirmed that this reaction sequence selectively delivers the more thermodynamically stable spiroketal (Figure 2). In the ^{1}H NMR spectrum H-10 in **32** resonates at δ 4.24, further downfield of H-10 in 10-*epi*-**32** that resonates at δ 4.02. This deshielding effect for H-10 in **32** is due to 1,3-diaxial interactions between H-10 and O1′. Based on this evidence, it is concluded that the thermodynamically favored spiroketal **32** is formed using this efficient multistep reaction sequence.

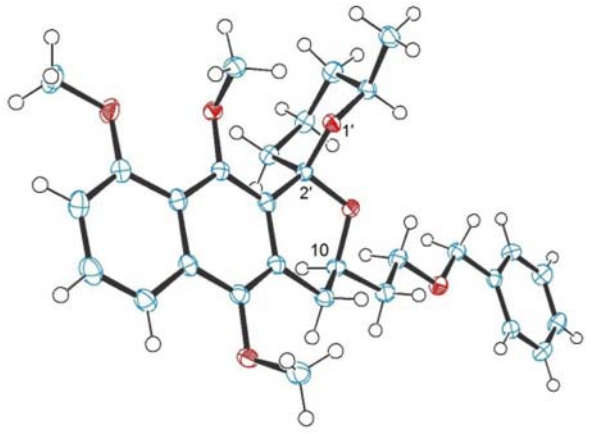
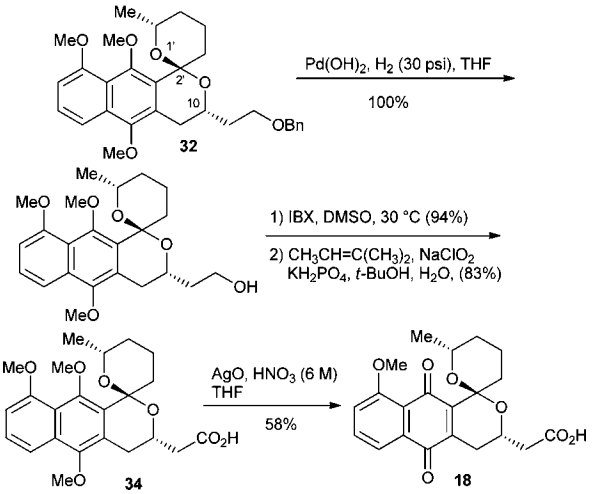


Figure 2. Crystal structure of 10-*epi*-**32**.

With the pyranonaphthoquinone-spiroketal skeleton assembled, synthetic work continued toward the fully elaborated griseusin B analogue **18** (Scheme 6). Debenzylation was effected using high pressure hydrogenation followed by two-step oxidation to afford the carboxylic acid **34** in high yield. Oxidative demethylation was unsuccessful using standard ceric ammonium nitrate conditions; however, use of freshly prepared AgO[18] gave **18** in a 58% yield, for which the stereochemistry is identical to that of the natural product **2**.

Scheme 6. Synthesis of Griseusin B Analogue, **18**



In summary, the synthesis of the griseusin B analogue **18** has been achieved. The synthesis involves a novel one-pot Hauser–Kraus annulation–methylation–double deprotection–spirocyclization reaction sequence starting from phthalide **20** and highly substituted enone **21**. Conversion of phthalide **20** and enone **21** to spiroketal **32** involves seven transformations that take place in one pot. To the best of our knowledge, this is the only reported example of a one-pot annulation–methylation–double deprotection–spirocyclization reaction to date. Studies toward the total synthesis of griseusin B **2** and other analogues continue in our laboratory.

Acknowledgment. The authors thank The University of Auckland for financial support (B.J.N.).

Supporting Information Available. Experimental procedures and spectroscopic and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) MMF conformer-AM1 geometry-HF energy (Spartan).

(18) Barbieri, G. A. *Ber. Dtsch. Chem. Ges. B* **1927**, *60B*, 2427.

The authors declare no competing financial interest.