Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 8888–8890

Total synthesis of (+)-kalafungin using a tandem Michael–Dieckmann approach

Christopher D. Donner*

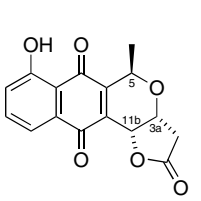
School of Chemistry, The University of Melbourne, Victoria 3010, Australia
Bio21 Molecular Science and Biotechnology Institute, The University of Melbourne, Victoria 3010, Australia

Received 18 September 2007; revised 3 October 2007; accepted 10 October 2007
Available online 14 October 2007

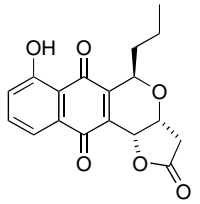
Abstract—A stereoselective synthesis of the antibiotic kalafungin **1** is reported. A key step involved the tandem Michael–Dieckmann reaction between methyl 2-methoxy-6-methylbenzoate **11** and the α,β-unsaturated lactone (*R*)-6-(2-(*tert*-butyldimethylsilyloxy)ethyl)-4-methoxy-5,6-dihydropyran-2-one **10**, which was prepared from (*S*)-aspartic acid. The C5 alkyl substituent was introduced by the use of methylmagnesium bromide and subsequent stereoselective reduction. A sequence of oxidations followed by acid-catalyzed epimerization delivered (+)-kalafungin **1**.

The pyranonaphthoquinone family of compounds is a class of antibiotics widely dispersed in nature, having been isolated from a variety of bacterial, fungal, plant and insect sources.[1] The various members of this group of natural products display an interesting array of biological activities.[2] For example, kalafungin **1** is an inhibitor of pathogenic fungi, protozoa, yeasts and Gram-negative bacteria as well as possessing cytotoxic activity. Frenolicin B **2** possesses antifungal and anticoccidial activity, whilst more complex substitution of the pyran ring is seen in griseusin A **3**, which shows modest cytotoxic activity. Although the mode of action of these antibiotics is not known with certainty it has been proposed that such naphthoquinones may undergo bioreduction to the corresponding hydroquinone followed by opening of the γ-lactone to generate a highly reactive *ortho*-quinone methide alkylating species.[3] Alternatively, quinones are also known to undergo one-electron reduction in vivo to generate reactive oxygen radicals via redox cycling that can cause oxidative stress leading to cell death.[4]

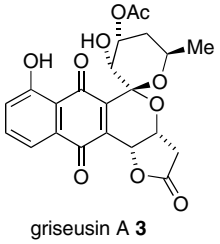
Kalafungin **1** was first isolated in 1968 from *Streptomyces tanashiensis*[5] and has since been isolated from numerous *Streptomyces* species. The structure and stereochemistry of **1** was determined by a combination of chemical[6] and spectroscopic[7] techniques. It is worth noting that the enantiomer of kalafungin, nanaomycin D **4**, is also known to occur naturally having been isolated from *Streptomyces rosa*.[8] Being the simplest γ-lactone-containing member of the pyranonaphthoquinone family, (+)-kalafungin **1** has been the subject of total synthesis using a variety of approaches. The first stereospecific synthesis was achieved by Tatsuta and co-workers[9] employing an enantiodivergent approach that delivered both kalafungin **1** and nanaomycin D **4** from a common optically active intermediate derived from L-rhamnose. More recently, Fernandes and Brückner[10] reported a stereoselective synthesis of kalafungin **1**, the



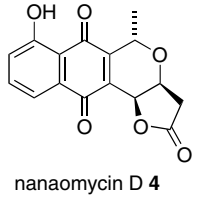
kalafungin **1**



frenolicin B **2**



griseusin A **3**



nanaomycin D **4**

* Tel.: +61 3 8344 2411; fax: +61 3 9347 8189; e-mail: cdonner@unimelb.edu.au

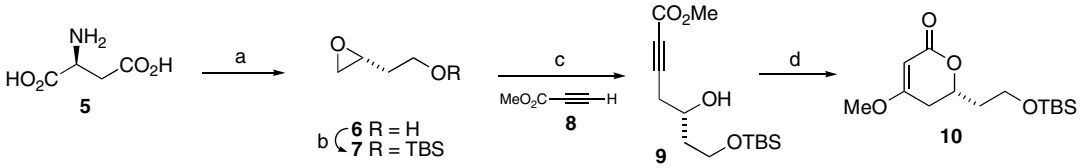
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.10.058

enantioselectivity (99.5% ee) being controlled by asymmetric dihydroxylation of a β,γ-unsaturated ester to generate the γ-lactone ring found in **1** followed by oxa-Pictet–Spengler cylization to form the tetracyclic framework.

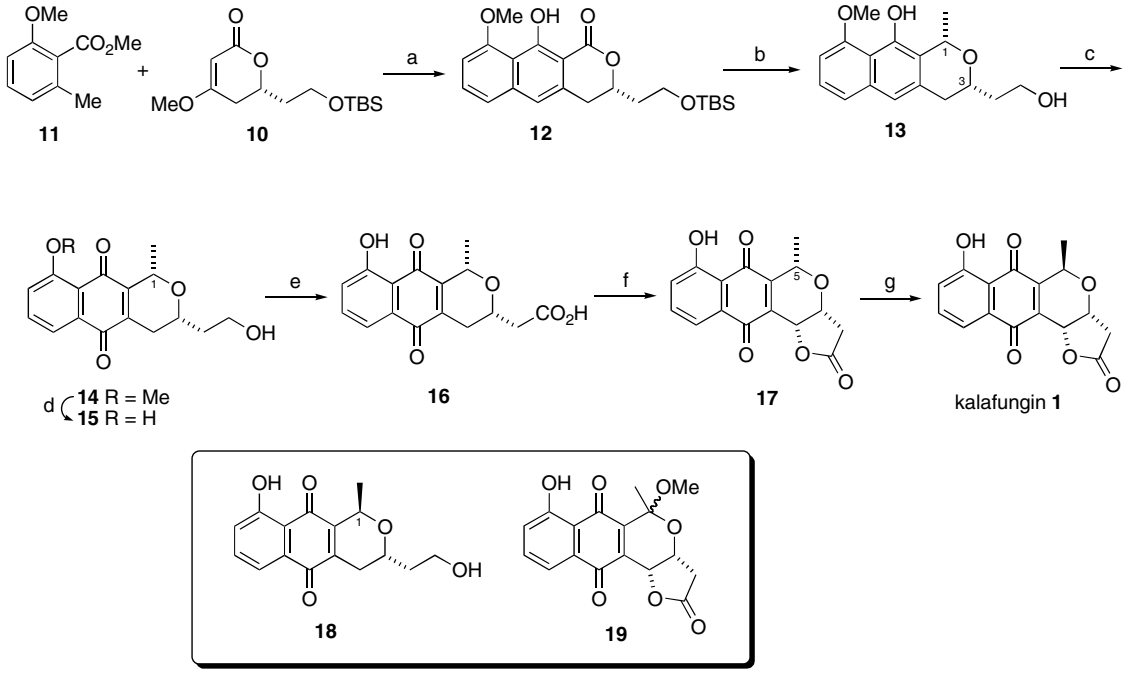
Despite there being many reported syntheses of pyranonaphthoquinone antibiotics,[11] the majority of approaches developed to date have delivered only racemic products and/or are not conveniently adaptable to the preparation of other naturally occurring members of this family or related analogues. Reported here is a stereoselective synthesis of (+)-kalafungin **1**, which uses (*S*)-aspartic acid as the source of chirality and employs a strategy that should be readily applicable to the preparation of a variety of C5 substituted analogues.

The synthesis of kalafungin **1** began with (*S*)-aspartic acid **5** (Scheme 1) that was converted to the (*R*)-epoxide **6** following standard procedures.[12] The (*R*)-epoxyalcohol **6** was subsequently protected as its *tert*-butyldimethylsilyl (TBS) ether **7** {$[\alpha]_D^{24}$ +11.0 (*c* 2.00, $CHCl_3$), lit.[13] $[\alpha]_D^{26}$ +12.5 (*c* 2.11, $CHCl_3$)} by exposure to TBSCl in dichloromethane. Treatment of epoxide **7** with the anion of methyl propiolate (**8**), using the Yamaguchi–Hirao protocol,[14] gave the acetylenic alcohol **9**. Exposure of acetylene **9** to sodium methoxide led to formation of the (*R*)-lactone **10** {$[\alpha]_D^{26}$ −46.7 (*c* 2.00, $CHCl_3$)} in an overall yield of 48% for the six steps from (*S*)-aspartic acid **5**.

The anion of toluate **11**, generated using LDA, underwent a tandem Michael–Dieckmann reaction with lactone **10** (Scheme 2) to deliver the novel naphthopyranone **12** in 52% yield (based on consumed lactone **10**). Introduction of the methyl group at C1 in **13** was achieved by the addition of excess methylmagnesium bromide to naphthopyranone **12**. The intermediate lactol was reduced stereoselectively using triethylsilane/trifluoroacetic acid to give the *cis*-pyran **13** as a single diastereoisomer. The 1,3-*cis* relationship between the C1 and C3 alkyl substituents is expected from the reported axial delivery of hydride under these reaction conditions[15] and was confirmed in the present case by the presence of a NOE correlation between the H-1 and H-3 protons, which adopt a 1,3-*pseudo*-diaxial arrangement. The (1*S*,3*S*)-naphthopyran **13** contains the complete carbon framework of kalafungin **1**.



Scheme 1. Reagents and conditions: (a) (i) $NaNO_2$, H_2SO_4, KBr, H_2O, 0 °C; 4 h (91%); (ii) $BH_3{\cdot}Me_2S$, THF, −30 °C to rt, 18 h (97%); (iii) K_2CO_3, CH_2Cl_2, 72 h (96%); (b) TBSCl, imidazole, CH_2Cl_2, 4 h (98%); (c) **8**, ^nBuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C, 30 min (72%); (d) NaOMe, MeOH, 16 h (80%).



Scheme 2. Reagents and conditions: (a) LDA, THF, −60 °C, 30 min (52%); (b) (i) MeMgBr, THF, 4 h; (ii) TFA, Et_3SiH, CH_2Cl_2, −78 °C, 1 h; (iii) THF, 2 M HCl, 16 h (64%, three steps); (c) (i) NBS, DMF, 16 h; (ii) CAN, H_2O, MeCN, 30 min (82%, two steps); (d) $AlCl_3$, CH_2Cl_2, 2 h (94%); (e) (i) $PhI(OAc)_2$, TEMPO, CH_2Cl_2, 20 h; (ii) $NaClO_2$, ^tBuOH, H_2O, NaH_2PO_4, 3 h (80%, two steps); (f) (i) O_2, MeOH, pyridine, 60 °C, 16 h; (ii) $BF_3{\cdot}Et_2O$, Et_3SiH, CH_2Cl_2, −45 °C, 30 min (65%, two steps); (g) H_2SO_4, PhH, 30 min (85%).

Final conversion of **13** to the natural product **1** required epimerization at C1 and a series of oxidations. Firstly, the naphthol was oxidized to quinone **14** using a 2-step process involving aromatic bromination using *N*-bromosuccinimide followed by oxidation of the resultant *p*-bromonaphthol with ceric ammonium nitrate (CAN). Demethylation of **14** with aluminium chloride[9] proceeded efficiently (94%) and selectively to give **15**. In contrast, the use of boron tribromide led to partial epimerization at C1, along with demethylation, to give a mixture of *cis*/*trans*-pyrans **15** and **18**. The primary alcohol in *cis*-pyran **15** was converted to a carboxylic acid using a conventional 2-step procedure involving, firstly, use of TEMPO/$PhI(OAc)_2$ to form the intermediate aldehyde followed by further oxidation with $NaClO_2$ to give the required acid **16**. Cyclization of carboxylic acids such as **16** to their corresponding γ-lactones has been reported to proceed efficiently under mild conditions in the presence of atmospheric oxygen via an intermediate quinone-methide.[16,17] However, this method was found to form, along with the desired γ-lactone **17**, product **19** resulting from further oxidation. Treatment of the crude mixture (~1:1) of **17** and **19** with $BF_3 \cdot Et_2O/Et_3SiH$ delivered 5-*epi*-kalafungin **17** as the exclusive product in 65% yield over the two steps.

Finally, inversion of the C5 configuration was effected by exposure of **17** to concentrated sulfuric acid.[10,16] This resulted in almost complete epimerization to the thermodynamically favoured 5,3a-*trans*-pyran **1** (93:7 mixture of **1**:**17**). Importantly, the spectroscopic data[18] for synthetic **1** prepared in this way from (*S*)-aspartic acid **5** was in good agreement with that reported for (+)-kalafungin **1**.[9]

In conclusion, this work constitutes a novel, stereoselective synthesis of (+)-kalafungin **1**. Additionally, the late-stage introduction of the C5 alkyl group should allow a variety of other substituents to be incorporated conveniently at this position by appropriate selection of Grignard reagent. This idea is currently being explored and should provide access to other members of this pyranonaphthoquinone family, including **2** and **3**.

Acknowledgements

Financial support from the Australian Research Council through the Centres of Excellence program is gratefully acknowledged. Professor Carl Schiesser, The University of Melbourne, is acknowledged for generous support of this work.

References and notes

1. Thomson, R. H. In *Naturally Occurring Quinones III: Recent Advances*, 3rd ed.; Chapman and Hall, 1987; Thomson, R. H. In *Naturally Occurring Quinones IV: Recent Advances*, 4th ed.; Blackie Academic and Professional, 1997.
2. Brimble, M. A.; Duncalf, L. J.; Nairn, M. R. *Nat. Prod. Rep.* **1999**, *16*, 267–281.
3. Moore, H. W. *Science* **1977**, *197*, 527–531.
4. Halliwell, B.; Gutteridge, M. C. In *Free Radicals in Biology and Medicine*, 3rd ed.; Oxford University Press, 1999; pp 564–572.
5. Bergy, M. E. *J. Antibiot.* **1968**, *21*, 454–457.
6. Hoeksema, H.; Krueger, W. C. *J. Antibiot.* **1976**, *29*, 704–709.
7. Duchamp, D. J. *American Crystallographic Association Summer Meeting*, 1968, paper 82.
8. Omura, S.; Tanaka, H.; Okada, Y.; Marumo, H. *J. Chem. Soc., Chem. Commun.* **1976**, 320–321.
9. Tatsuta, K.; Akimoto, K.; Annaka, M.; Ohno, Y.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1699–1706.
10. Fernandes, R. A.; Brückner, R. *Synlett* **2005**, 1281–1285.
11. For a comprehensive review, see: Brimble, M. A.; Nairn, M. R.; Prabaharan, H. *Tetrahedron* **2000**, *56*, 1937–1992.
12. Volkmann, R. A.; Kelbaugh, P. R.; Nason, D. M.; Jasys, V. J. *J. Org. Chem.* **1992**, *57*, 4352–4361.
13. Mori, K.; Ikunaka, M. *Tetrahedron* **1984**, *40*, 3471–3479.
14. Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391–394.
15. (a) Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Chem. Soc., Chem. Commun.* **1986**, 1568–1569; (b) Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Org. Chem.* **1987**, *52*, 1273–1276.
16. Li, T.; Ellison, R. H. *J. Am. Chem. Soc.* **1978**, *100*, 6263–6265.
17. (a) Hoffmann, B.; Schonebaum, A.; Lackner, H. *Liebigs Ann. Chem.* **1993**, 333–342; (b) Masquelin, T.; Hengartner, U.; Streith, J. *Synthesis* **1995**, 780–786.
18. *Selected spectroscopic data for synthetic* **1**: ^1H NMR (500 MHz, $CDCl_3$) δ 1.57 (3H, d, *J* 6.8 Hz), 2.71 (1H, d, *J* 17.7 Hz), 2.97 (1H, dd, *J* 17.7 and 5.2 Hz), 4.69 (1H, dd, *J* 5.2 and 3.0 Hz), 5.09 (1H, q, *J* 6.8 Hz), 5.26 (1H, d, *J* 3.0 Hz), 7.31 (1H, dd, *J* 8.3 and 1.5 Hz), 7.67 (1H, dd, *J* 8.3 and 7.6 Hz), 7.71 (1H, dd, *J* 7.6 and 1.5 Hz), 11.84 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.6, 36.9, 66.2, 66.4, 68.6, 114.8, 119.8, 124.9, 131.5, 135.1, 137.2, 149.7, 161.9, 173.9, 181.5, 188.0.