



Pergamon

Total synthesis of atroviridin

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Abstract—A total synthesis of atroviridin (**1**) based on biosynthetic principles is presented. The tetracyclic xanthone structure of the natural product was constructed by coupling aryl bromide **8** with aldehyde **7** and subsequent intramolecular conjugate addition on a quinone precursor. Bromide **8** was produced from aldehyde **9** via a sequence of steps involving Baeyer–Villiger oxidation and Claisen cyclization. © 2003 Elsevier Science Ltd. All rights reserved.

Atroviridin (**1**)¹ (Fig. 1) is a tetracyclic polyhydroxylated xanthone recently isolated from the stem bark of *Garcinia atroviridis*, a lofty tree indigenous to Thailand. Although the precise biological mode of action of this natural product has not yet been reported, it is noted that a decoction of the leaves of the parent tree has been traditionally used for the treatment of earache.

From a structural standpoint, atroviridin (**1**) belongs to a growing family of xanthone and xanthonoid natural

products isolated from *Garcinia*-related tropical plants.² Representative members of this family include osajaxanthone (**2**),³ morellin (**3**),⁴ morellic acid (**4**)⁵ and lateriflorone (**5**)⁶ (Fig. 1). All these compounds are presumed to derive from benzophenone or benzophenone-like intermediates generated by means of a mixed shikimate–acetate biosynthetic pathway that, upon an intramolecular oxidative coupling or conjugate addition, produce a common xanthone scaffold.⁷ A series of plant specific oxygenations, prenylations and pericyclic reactions are postulated to bring about the final structure and are accountable for the observed biological activities of these natural products. In continuation with our synthetic studies in this area,⁸ we present herein the first total synthesis of atroviridin (**1**).

In step with the presumed biosynthetic pathway, atroviridin was thought to be accessible from benzophenone-like intermediate **6** through an intramolecular conjugate addition (Fig. 2). Moreover, disconnection across the C9–C9a bond (xanthone numbering) suggests a synthetic route toward **6** based on coupling of aldehyde **7** with aryl bromide **8**. The latter compound was envisioned to arise from protected hydroquinone **9** by a sequence of steps including a Baeyer–Villiger oxidation (introduction of O1 atom) and a Claisen rearrangement (construction of C2–C4' bond).¹⁰ Reduction of this plan to the synthesis of **1** is shown in Schemes 1 and 2.

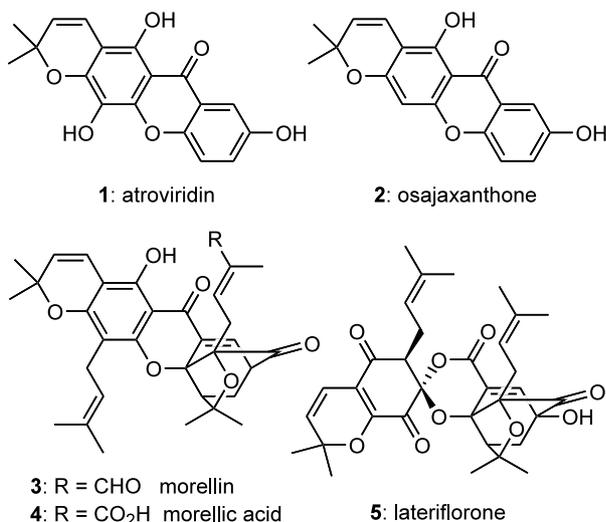


Figure 1. Selected xanthones from the *Garcinia* family of plants.

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The synthesis of aryl bromide **8** is shown in Scheme 1 and began with commercially available benzaldehyde **10**. Regioselective bromination of **10** at the 9a position (atroviridin numbering) with a slight excess of bromine in acetic acid produced adduct **9** in 45% yield.⁹ Baeyer–

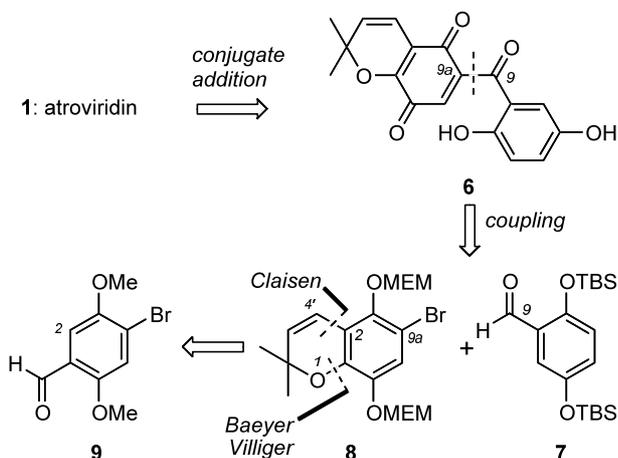
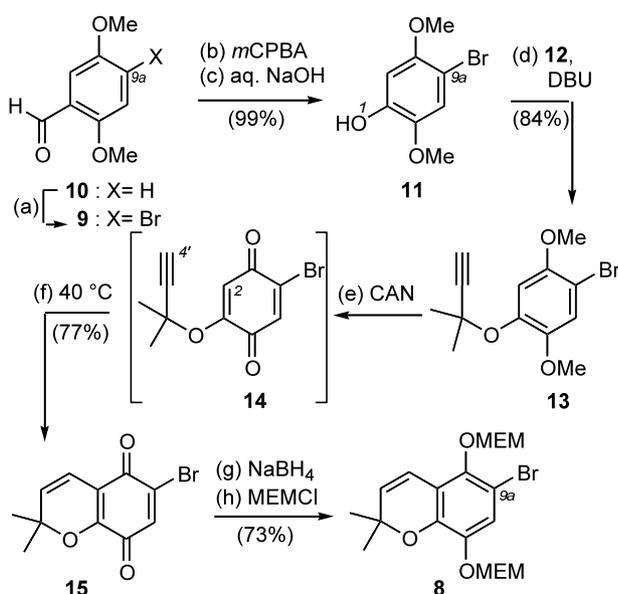


Figure 2. Strategic bond disconnections of atroviridin (1).

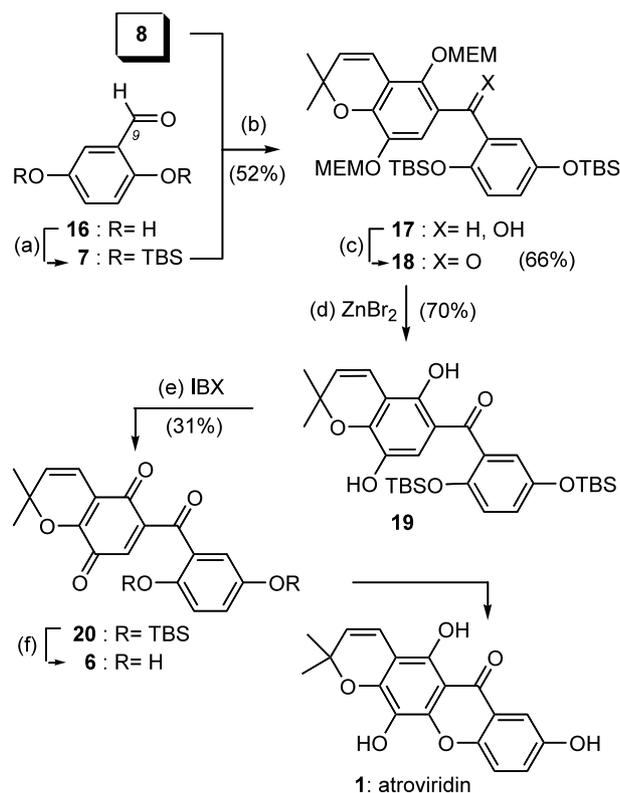


Scheme 1. Reagents and conditions: (a) 1.1 equiv. Br_2 , AcOH, 4 h, 25°C, 45%; (b) 1.3 equiv. *m*-CPBA, CH_2Cl_2 , 4 h, 25°C; (c) 10% NaOH (aq.) in MeOH, 1 h, 25°C, 99% (over two steps); (d) 1.2 equiv. 1,1-dimethylprop-2-ynyl methyl carbonate (**12**), 1.3 equiv. DBU, 0.03 mol% CuCl_2 , CH_3CN , 6 h, 0°C, 84%; (e) 2.5 equiv. CAN, 40% H_2O in CH_3CN , 0.5 h, 25°C; (f) PhCH_3 , 0.5 h, 40°C, 77% overall; (g) 2.2 equiv. NaBH_4 , 22 equiv. AcOH, THF, 0.5 h, 25°C; (h) 2.5 equiv. MEMCl, 2.8 equiv. DIPEA, CH_2Cl_2 , 2 h, 0°C, 73% (over two steps).

Villiger oxidation of **9** followed by hydrolysis of the resulting formate ester under basic conditions afforded phenol **11** in 99% yield.¹¹ This compound was *O*-alkylated with 1,1-dimethylprop-2-ynyl methyl carbonate (**12**) using DBU and catalytic CuCl_2 in acetonitrile to produce alkyne **13** (84% yield).¹² Aiming to produce quinone **14** we subjected methyl hydroquinone **13** to a variety of oxidative demethylation conditions, including cerium ammonium nitrate (CAN) or CoF_3 . Although quinone **14** could be isolated, it was always found to be contaminated with small amounts of cyclized adduct **15**

which was formed upon sitting, presumably via a spontaneous Claisen cyclization.¹³ Since this cyclization event was found to be somewhat slow, requiring up to 2 days depending upon batch size, an improved procedure was developed en route to chromenequinone **15**. According to the improved protocol, hydroquinone **13** was treated with CAN in 40% aqueous acetonitrile transiently producing quinone **14**, which was extracted from the orange reaction mixture and, without further purification, was heated at 40°C in toluene. This reaction temperature was sufficient for the complete conversion of compound **13** to the red-colored chromenequinone **15** in 77% yield over two steps. We also studied the effect of CoF_3 on methyl ether **13** in 10% H_2O /dioxane.¹⁴ Under these conditions the reaction was considerably longer and offered no advantages over the previously described CAN-mediated oxidation. Reduction of quinone **15** with NaBH_4 and AcOH in THF yielded the resulting hydroquinone¹⁵ which was immediately converted to its MEM ether **8** using MEMCl and DIPEA (73% yield over two steps).¹⁶

Completion of the total synthesis of atroviridin (1) by union of bromide **8** with aldehyde **7** is shown in Scheme 2. To this end, commercially available 2,5-dihydroxy



Scheme 2. Reagents and conditions: (a) 2.2 equiv. TBSCl, 2.5 equiv. imid, CH_2Cl_2 , 4 h, 25°C, 62%; (b) 1.3 equiv. *n*-BuLi, Et_2O , 1 h, -78 to 0°C, 52%; (c) 1.5 equiv. Dess–Martin periodinane, CH_2Cl_2 , 1 h, 25°C, 66%; (d) 5.0 equiv. ZnBr_2 , CH_2Cl_2 , 4 h, 25°C, 70%; (e) 2.5 equiv. IBX, 5% DMF in CHCl_3 , 4 h, 25°C, 31%; (f) 2.2 equiv. TBAF, THF, 1 h, 25°C, 40%.

benzaldehyde (**16**) was protected as the corresponding silyl ether **7** and subsequently alkylated with the lithium salt of **8** to afford benzylic alcohol **17** in 52% yield. Oxidation of **17** with Dess–Martin periodinane in CH₂Cl₂ gave rise to benzophenone **18** in 66% yield.¹⁷ Deprotection of the MEM ethers of **18** was accomplished using an excess of ZnBr₂ in CH₂Cl₂ producing hydroquinone **19** in 70% yield.¹⁶ The stage was now set for an oxidation of the hydroquinone ring and subsequent conjugate addition. Surprisingly, the desired oxidation proved to be more problematic than expected. Mild heterogeneous oxidants, such as MnO₂ were found to be completely ineffective.¹⁸ After several experimental attempts we found that the best conditions involved treatment of **19** with IBX in 5% DMF/CHCl₃ at ambient temperature producing quinone **20** in 31% yield.¹⁹ It was also possible to effect the same oxidation with Dess–Martin periodinane in CH₂Cl₂. Nonetheless, the Dess–Martin oxidation did not offer an increase in yield or any other distinct advantage over the IBX oxidation except for a more rapid reaction time. With the red-colored quinone **20** in hand, the final deprotection and sequential cyclization could be tested. Along these lines, treatment of **20** with TBAF in THF produced a brown solution which, over a 1 h period, became increasingly yellow. This hypsochromic shift suggested that the initially formed colored quinone **6** could react in situ to produce a less chromophoric hydroquinone structure. Indeed, isolation, followed by spectroscopic and analytical characterization of the major product of this reaction confirmed the total synthesis of atroviridin (**1**).

In conclusion, we have presented an efficient and convergent synthesis of atroviridin (**1**), a member of the xanthone and xanthonoid natural products pool isolated from the *Garcinia* species of tropical plants. Our strategy highlights the use of a cerium ammonium nitrate-mediated oxidative demethylation and tandem Claisen cyclization to form chromenequinone **15**. This spontaneously occurring Claisen rearrangement is rare in the literature and this occurrence may in fact be the only case in which it has been used in the context of the total synthesis of a natural product. Additionally, the final deprotection protocol with concomitant annulation to form atroviridin (**1**) mirrors a proposed biosynthetic pathway for xanthone and xanthonoid natural products.

Acknowledgements

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References

- (a) Kosin, J.; Ruangrunsi, N.; Ito, C.; Furukawa, H. *Phytochemistry* **1998**, *47*, 1167–1168; (b) Parmana, D.; Lajis, N. H.; Mackeen, M. M.; Ali, A. M.; Aimi, N.; Kitajima, M.; Takayama, H. *J. Nat. Prod.* **2001**, *64*, 976–979.
- The *Garcinia* species belongs to the Guttiferae family of tropical plants (also known as the Clusiaceae family). For general references on natural products isolated from these plants, see: (a) Ollis, W. D.; Redman, B. T.; Sutherland, I. O.; Jewers, K. *J. Chem. Soc., Chem. Commun.* **1969**, 879–880; (b) Kumar, P.; Baslas, R. K. *Herba Hungarica* **1980**, *19*, 81–91; (c) Thoison, O.; Fahy, J.; Dumontet, V.; Chiaroni, A.; Riche, C.; Tri, M. V.; Sevenet, T. *J. Nat. Prod.* **2000**, *63*, 441–446.
- (a) Wolfrom, M. L.; Dickey, E. E.; McWain, P.; Thompson, A.; Looker, J. H.; Windrath, O. M.; Komitsky, F., Jr. *J. Org. Chem.* **1964**, *29*, 689–691; (b) Wolfrom, M. L.; Komitsky, F., Jr.; Looker, J. H. *J. Org. Chem.* **1965**, *30*, 144–149.
- (a) Rao, B. S. *J. Chem. Soc. (C)* **1937**, 853–857; (b) Kartha, G.; Ramachandran, G. N.; Bhat, H. B.; Nair, P. M.; Raghavan, V. K. V.; Venkataraman, K. *Tetrahedron Lett.* **1963**, *4*, 459–472.
- Karanjgaongar, C. G.; Nair, P. M.; Venkataraman, K. *Tetrahedron Lett.* **1966**, *7*, 687–691.
- Kosela, S.; Cao, S.-G.; Wu, X.-H.; Vittal, J. J.; Sukri, T.; Masdianto; Goh, S.-H.; Sim, K.-Y. *Tetrahedron Lett.* **1999**, *40*, 157–160.
- (a) Roberts, J. C. *Chem. Rev.* **1961**, *61*, 591–605; (b) Carpenter, I.; Locksley, H. D.; Scheinmann, F. *Phytochemistry* **1969**, *8*, 2013–2026; (c) Bennett, G. J.; Lee, H.-H. *J. Chem. Soc., Chem. Commun.* **1988**, 619–620; (d) Quillinan, A. J.; Scheinmann, F. *J. Chem. Soc., Chem. Commun.* **1971**, 966–967.
- Tisdale, E. J.; Chowdhury, C.; Vong, B. G.; Li, H.; Theodorakis, E. A. *Org. Lett.* **2002**, *4*, 909–912.
- Sardessai, M. S.; Abramson, H. N. *Org. Prep. Proceed. Int.* **1991**, *23*, 419–424.
- (a) Claisen, L. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 3157. For recent and selected reviews on Claisen rearrangement, see: (b) Nowicki, J. *Molecules* **2000**, *5*, 1033–1050; (c) Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43–50; (d) Gajewski, J. J. *Acc. Chem. Res.* **1997**, *30*, 219–225; (e) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423–1452; (f) Wipf, P. In *Comprehensive Org. Synth.*; Trost, B. M.; Fleming, I., Eds.; **1991**, *5*, 827.
- Wriede, U.; Fernandez, M.; West, K. F.; Harcourt, D.; Moore, H. W. *J. Org. Chem.* **1987**, *52*, 4485–4489.
- Godfrey, J. D., Jr.; Mueller, R. H.; Sedergran, T. C.; Soundararajan, N.; Colandrea, V. J. *Tetrahedron Lett.* **1994**, *35*, 6405–6408.
- The spontaneous propargylic Claisen rearrangement on quinones has previously been noted but its occurrence in the literature appears to be limited. For one reference, see: Brown, P. E.; Lewis, R. A.; Waring, M. A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2979–2988.
- (a) Tomatsu, A.; Takemura, S.; Hashimoto, K.; Nakata, M. *Synlett* **1999**, 1474–1476; (b) Knolker, H.-J.; Baum, E.; Reddy, K. R. *Tetrahedron Lett.* **2000**, *41*, 1171–1174.
- Pugh, C. *Org. Lett.* **2000**, *2*, 1329–1331.
- Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, *17*, 809–812.
- Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

18. (a) Ling, T.; Xiang, A. X.; Theodorakis, E. A. *Angew. Chem., Int. Ed.* **1999**, *38*, 3089–3091; (b) Ling, T.; Poupon, E.; Rueden, E. J.; Theodorakis, E. A. *J. Am. Chem. Soc.* **2002**, *124*, 12261–12267.
19. (a) Wirth, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 2812–2814; (b) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2001**, *123*, 3183–3185; (c) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258; (d) Magdziak, D.; Rodriguez, A. A.; Van De Water, R. W.; Pettus, T. R. R. *Org. Lett.* **2002**, *4*, 285–288; (e) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001–3003.