Total Synthesis of Cytosporone B

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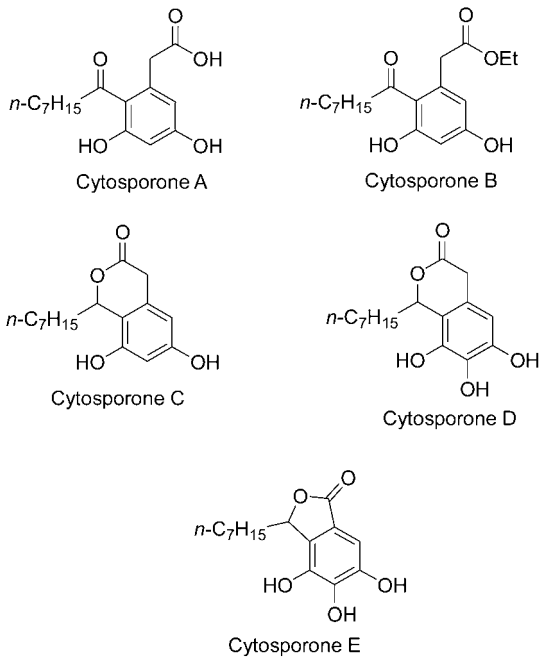
The total synthesis of Cytosporone B, a naturally occurring agonist for Nur77, has been accomplished. The key steps are the sequential Grignard reaction and Lemieux-van Rudloff oxidation followed by a deprotection of the methyl aromatic ether to phenol and subsequent Friedel-Crafts acylation.

Keywords Cytosporone B, total synthesis, agonist, antitumor agents

Introduction

Cytosporone B, isolated from *Cytospora* sp. CR200 and *Dothiorella* sp. HTF3, belongs to a family including Cytosporones A, B, C, D and E (Scheme 1).[1] Some of them display antibacterial activity.[1-3] Particularly, a recent excellent report by Wu *et al.*[4] has revealed that Cytosporone B acted as an agonist for Nur77. Nuclear receptors play important roles in numerous biological processes such as cell proliferation, differentiation, apoptosis, metabolism and development.[5-8] Nur77 is one of the orphan receptors which act as transcription factors to regulate the expression of target genes by targeting their response elements.[9-12] However, a physiological ligand for Nur77 has not been identified. Remarkably, Cytosporone B is a naturally occurring agonist for Nur77.[4] It has a strong affinity for Nur77 and stimulates the transactivational activity of Nur77. Moreover, it increases Nur77-mediated induction of apoptosis, increases growth inhibition of xenograft tumors in nude mice, and enhances gluconeogenesis in mouse liver. Importantly, Cytosporone B does not exert any of these effects on Nur77-null mice or cells. These results reveal that Cytosporone B may be useful in the development of new therapeutic drugs to treat cancer and hypoglycemia.[4] The novel structures of Cytosporone B combining with remarkable biological activity and lack of availability from natural sources have attracted interest from chemists for its total synthesis. In the following we report on the total synthesis of this compound.

Scheme 1 Structures of Cytosporones A—E



Results and discussion

The key to the synthesis of the Cytosporone B was the construction of the 2-phenylacetic acid skeleton. Many methods have been reported, such as the self-condensation of dimethyl 1,3-acetonedicarboxylate,[13,14] decarboxylation of 2-phenylmalonic acids,[15-18] and oxidation of allylbenzene.[19-21] Progress in the total synthesis of Cytosporone B has been made recently. Zhang *et al.*[22] constructed the 2-phenylacetic acid skeleton via hydrolysis using 2-phenylacetonitrile, which was prepared from benzyl methanesulfonate and sodium cyanide. Such synthetic route has been shown to be effective in generating the 2-(dihydroxyphenyl)acetic acids. However, this process needs a long synthetic

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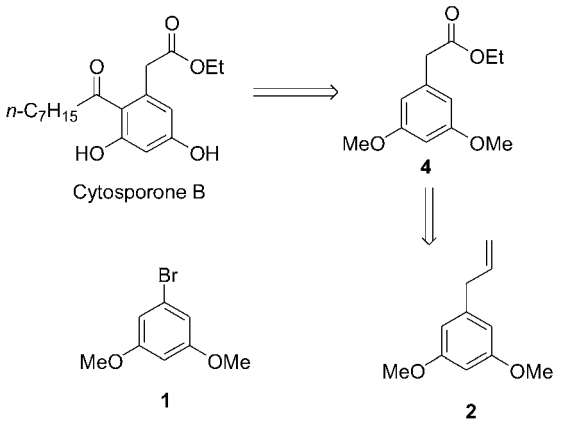
route and hypertoxic reagent. A general method for the oxidation of olefins is using $KMnO_4$ together with $NaIO_4$ as the oxidants. The reaction conditions are mild and the protocol is convenient. Therefore, we chose the oxidation of allylbenzene to prepare the 2-phenylacetic acid skeleton.

The retrosynthetic analysis is as follows (Scheme 2). Cytosporone B would be synthesized by deprotection of ethyl 2-(3,5-dimethoxy-2-octanoylphenyl)acetate generated via a Friedel-Crafts acylation. The key intermediate **4** would be obtained by an Grignard reaction of 1-bromo-3,5-dimethoxybenzene (**1**) with 3-bromoprop-1-ene, followed by sequential oxidation and esterification of the olefin **2**.

Scheme 2 Retrosynthetic analysis of Cytosporone B

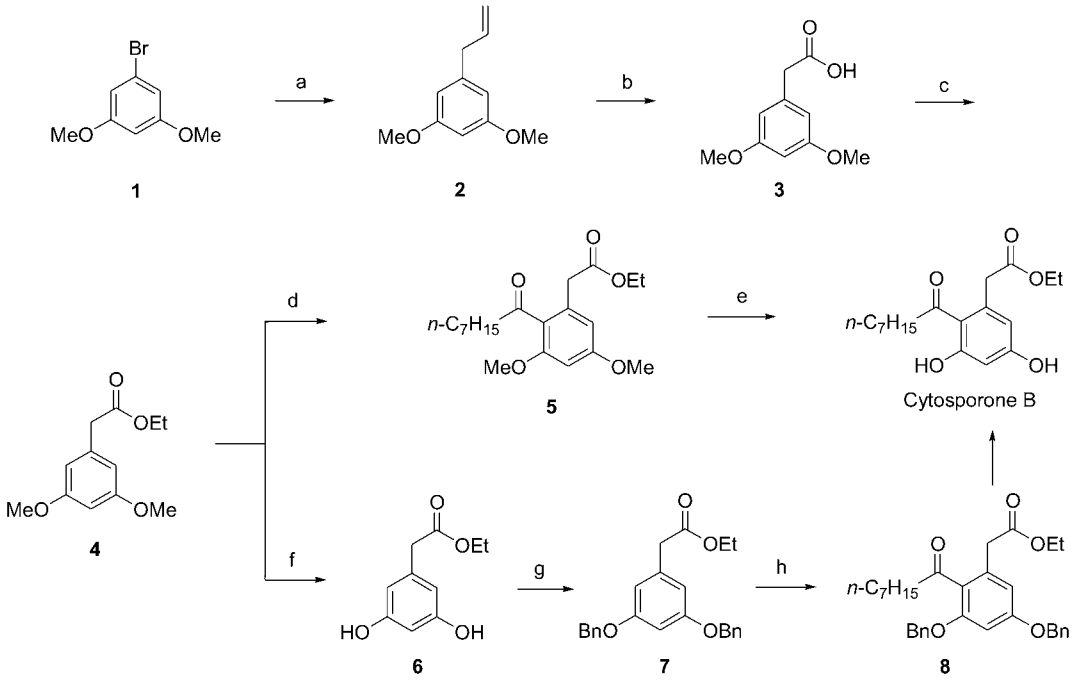


The synthetic routine is shown in Scheme 3. The first step in the synthesis of 1-allyl-3,5-dimethoxybenzene (**2**) was the Grignard reaction of 1-bromo-3,5-dimethoxybenzene. In order to construct the 2-phenylacetic acid moiety, an oxidation reaction of the compound **2** was envisaged. The attempted oxidation by means of $RuCl_3/NaIO_4$ was unsuccessful.[20] Finally, a Lemieux-van Rudloff oxidation[19] (substoichiometric amounts of $KMnO_4$ together with an excess of $NaIO_4$) allowed the isolation of acid **3** in moderate yield (51%, two steps).

With the key intermediate **4** now available by the oxidation and esterification, the sequential Friedel-Crafts acylation and deprotection were performed subsequently. The Friedel-Crafts reaction proceeded smoothly enough, with 86% yield of the purified product. However, the subsequent phenolic deprotection was problematic. Initially, an attempt to deprotect ethyl 2-(3,5-dimethoxy-2-octanoylphenyl)acetate (**5**) using BBr_3 failed. Next, the ether was deprotected to the phenol by refluxing with HBr/AcOH.[23] Unfortunately, the reaction conditions chosen did not yield the product. Another attempt was then made with $AlCl_3$. Despite an earlier report[24] of a similar reaction, the reagent could not give the deprotected product yet. The reaction proceeded difficultly and hence was abandoned.

A benzyl ether protecting group for the phenol was used next, simply because the benzyl group could be deprotected in mild reaction conditions. The ether in **4** was deprotected first to phenol **6** using BBr_3, followed

Scheme 3



Reagents and conditions: (a) Mg, I_2, THF, 3-bromoprop-1-ene, r.t., 3 h; (b) $KMnO_4$, $NaIO_4$, K_2CO_3, *t*-BuOH/H_2O, r.t., 4 h; (c) DCC, EtOH, r.t., 3 h; (d) $AlCl_3$, 1,2-dichloroethane, octanoyl chloride, 0 ℃ to r.t., 8 h; (e) BBr_3, CH_2Cl_2, 0 ℃ to r.t., 10 h; or 57% HBr/AcOH, reflux, 8 h; or DCM, $AlCl_3$ (6.00 equiv.), 0 ℃ to r.t., 12 h; (f) BBr_3, CH_2Cl_2, 0 ℃ to r.t., 10 h; (g) BnBr, K_2CO_3, DMF, 60 ℃, 5 h; (h) $AlCl_3$, 1,2-dichloroethane, octanoyl chloride, 0 ℃ to r.t., 8 h; (i) H_2, 10% Pd/C, 4 h

by etherification with benzyl bromide to yield the intermediate **7** (56% yield, two steps). The hydroxyl protection step was followed by an attempt to acylation of this protected phenol with octanoyl chloride catalyzed by $AlCl_3$ (83% yield). Finally, the debenzylation of ethyl 2-(3,5-bis(benzyloxy)-2-octanoylphenyl)acetate (**8**) under H_2 proceeded very smoothly (95% yield) and very pure Cytosporone B was obtained.[25] Characterization data were in complete agreement with the existing literature.[1]

Conclusion

In summary, the total synthesis of Cytosporone B has been achieved from 1-bromo-3,5-dimethoxybenzene. It is possible to extend the present protocol developed for the synthesis of other natural products with the 2-phenylacetic acid skeleton. The synthesis is amenable to large scale, and a similar strategy will allow the synthesis of analogs of Cytosporones for further structure-activity relationship study.

References and note

1 Brady, S. F.; Wagenaar, M. M.; Singh, M. P.; Janso, J. E.; Clardy, J. *Org. Lett.* **2000**, *2*, 4043.
2 Hall, J. D.; Duncan-Gould, N. W.; Siddiqi, N. A.; Kelly, J. N.; Hoeferlin, L. A.; Morrison, S. J.; Wyatt, J. K. *Bioorg. Med. Chem.* **2005**, *13*, 1409.
3 Ohzeki, T.; Mori, K. *Biosci. Biotechnol. Biochem.* **2003**, *67*, 2584.
4 Zhan, Y.; Du, X.; Chen, H.; Liu, J.; Zhao, B.; Huang, D.; Li, G.; Xu, Q.; Zhang, M.; Weimer, B. C.; Chen, D.; Cheng, Z.; Zhang, L.; Li, Q.; Li, S.; Zheng, Z.; Song, S.; Huang, Y.; Ye, Z.; Su, W.; Lin, S.-C.; Shen, Y.; Wu, Q. *Nat. Chem. Biol.* **2008**, *4*, 548.
5 Winoto, A.; Littman, D. R. *Cell* **2002**, *109*(Suppl.), S57.
6 Giguere, V. *Endocr. Rev.* **1999**, *20*, 689.
7 Katayama, K.; Wada, K.; Nakajima, A.; Kamisaki, Y.; Mayumi, T. *J. Pharmacol. Sci.* **2005**, *97*, 171.
8 Zou, C. P.; Clifford, J. L.; Xu, X. C.; Sacks, P. G.; Chambon, P.; Hong, W. K.; Lotan, R. *Cancer Res.* **1994**, *54*, 5479.
9 Philips, A.; Lesage, S.; Gingras, R.; Maira, M. H.; Gauthier, Y.; Hugo, P.; Drouin, J. *Mol. Cell Biol.* **1997**, *17*, 5946.
10 Philips, A.; Maira, M.; Mullick, A.; Chamberland, M.; Lesage, S.; Hugo, P.; Drouin, J. *Mol. Cell Biol.* **1997**, *17*, 5952.
11 Wilson, T. E.; Fahrner, T. J.; Johnston, M.; Milbrandt, J. *Science* **1991**, *252*, 1296.
12 Davis, I. J.; Lau, L. F. *Mol. Cell Biol.* **1994**, *14*, 3469.
13 Viviani, F.; Gaudry, M.; Marquet, A. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1255.
14 Stone, M. J.; Maplestone, R. A.; Rahman, S. K.; Williams, D. H. *Tetrahedron Lett.* **1991**, *32*, 2663.
15 Zeevaart, J. G.; Parkinsona, C. J.; de Koningb, C. B. *Tetrahedron Lett.* **2004**, *45*, 4261.
16 Özdemir, I.; Yiğit, M.; Çetinkaya, E.; Çetinkaya, B. *Tetrahedron Lett.* **2004**, *45*, 5823.
17 Xu, X.-X.; Wang, M.; Liu, Q.; Pan, L.; Zhao, Y.-L. *Chin. J. Chem.* **2006**, *24*, 1431.
18 Montazerozohori, M.; Nasr-Esfahani, M.; Akhlaghi, P. *Chin. J. Chem.* **2009**, *27*, 1007.
19 Detterbeck, R.; Hesse, M. *Helv. Chim. Acta* **2003**, *86*, 343.
20 Bauta, W. E.; Lovett, D. P.; Cantrell, W. R., Jr.; Burke, B. D. *J. Org. Chem.* **2003**, *68*, 5967.
21 Queffélec, C.; Bailly, F.; Cotelle, P. *Synthesis* **2006**, 768.
22 Zhang, H.-Q.; Zeng, H.-N.; Huang, P.-Q.; Wu, Q.; Shen, Y.-M. *CN101402573*, **2009** [*Chem. Abstr.* **2009**, *150*, 472417] (in Chinese).
23 Cammidge, A. N.; King, A. S. H. *Tetrahedron Lett.* **2006**, *47*, 5569.
24 Mondal, M.; Puranik, V. G.; Argade, N. P. *J. Org. Chem.* **2007**, *72*, 2068.
25 Analytical data for Cytosporone B: yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 6.35 (d, J=2.1 Hz, 1H), 6.32 (d, J=2.1 Hz, 1H), 4.08 (q, J=7.2 Hz, 2H), 3.57 (s, 2H), 2.78 (t, J=7.2 Hz, 2H), 1.64—1.55 (m, 2H), 1.28—1.21 (m, 8H), 1.20 (t, J=7.2 Hz, 3H), 0.83 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 206.7, 171.3, 164.3, 160.4, 136.6, 116.4, 112.6, 103.1, 61.5, 43.3, 47.1, 31.6, 29.1, 29.0, 24.9, 22.5, 14.1, 14.0; MS (ESI) *m/z*: 323.1 $[M+H]^+$; HRMS (ESI) calcd for $C_{18}H_{27}O_5$ $[M+H]^+$ 323.1858, found 323.1860.

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