Pergamon

Tetrahedron Letters 41 (2000) 465–469

TETRAHEDRON LETTERS

Studies toward the total synthesis of Sch 202596, an antagonist of the galanin receptor subtype GalR1: synthesis of geodin, the spirocoumaranone subunit of Sch 202596

Tadashi Katoh * and Osamu Ohmori

Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229-0012, Japan

Received 22 September 1999; revised 14 October 1999; accepted 18 October 1999

Abstract

An efficient synthesis of (±)-geodin [(±)-**2**] corresponding to the spirocoumaranone subunit of Sch 202596 (**1**) was accomplished in a convergent manner by utilizing coupling reaction of the aryl aldehyde **5** with the aryl bromide **6** and oxidative spirocyclization of the benzophenone **4** as the key steps. The aromatic segments **5** and **6** were prepared from commercially available methyl 3,5-dihydroxybenzoate (**7**) and 5-methylresorcinol (**8**), respectively.

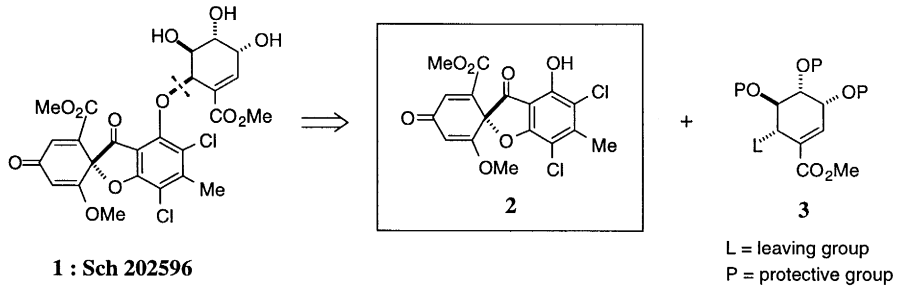
Keywords: antibiotics; biomimetic reactions; coupling reactions; cyclization; spiro compounds.

Sch 202596 (**1**), isolated from a fungal fermentation culture *Aspergillus* sp. by the Schering–Plough research group in 1997, has been shown to be the first non-peptidic antagonist of the galanin receptor subtype GalR1.[1–3] Since the use of a galanin receptor antagonist can inhibit galanin-induced feeding,[4] this natural product is anticipated to be a promising agent for the treatment of feeding disorders involving overeating and obesity.[1,5] The gross structure of **1** was revealed by extensive spectroscopic studies to have a novel spirocoumaranone skeleton connected with a highly oxygenated cyclohexene ring via an ether linkage.[1,6] Its remarkable biological properties as well as its unique structural features make **1** an exceptionally intriguing and timely target for total synthesis.

We embarked on a project directed at the total synthesis of **1** and its congeners with the aim of exploring the structure–activity relationships. Our synthetic strategy for **1** was designed as shown in Scheme 1, in which the ether linkage in **1** was disconnected retrosynthetically to give the spirocoumaranone subunit **2** and the cyclohexene subunit **3**. Incidentally, the spirocoumaranone subunit **2** is identical with the known antifungal antibiotic (+)-geodin.[7] To the best of our knowledge, the total synthesis of **2** has not been reported to date. In this communication, we wish to report an efficient and facile method for the synthesis of (±)-geodin [(±)-**2**].

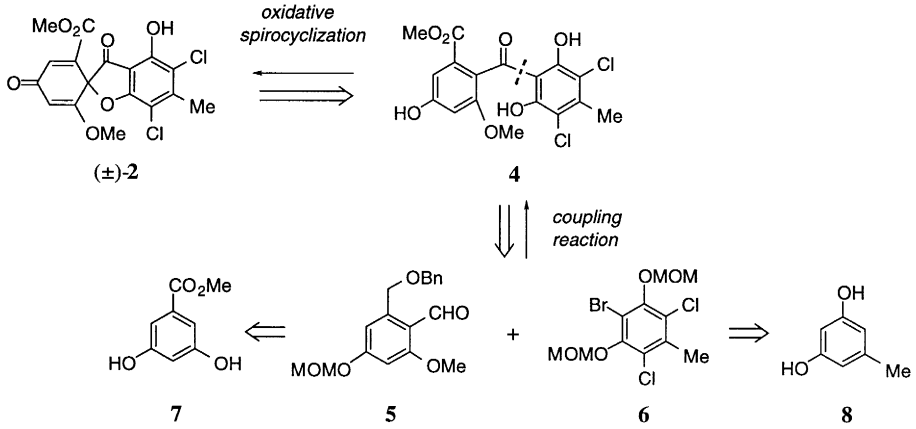
* Corresponding author. Fax: +81-427-49-7631; e-mail: takatoh@alles.or.jp (T. Katoh)

0040-4039/00/$ - see front matter
PII: S0040-4039(99)02005-5



Scheme 1. Synthetic plan for Sch 202596 (**1**)

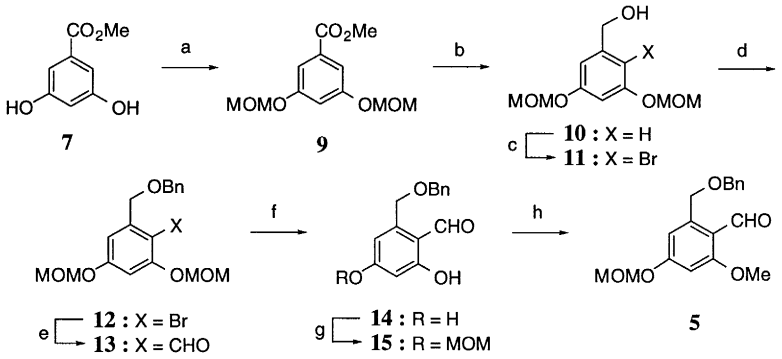
The synthetic plan for (±)-geodin [(±)-**2**] is outlined in Scheme 2, which features the biogenetic-type oxidative spirocyclization[8,9] of the tetra-*ortho*-substituted benzophenone **4** and the coupling reaction of the tetrasubstituted aryl aldehyde **5** with the fully substituted aryl bromide **6** as the key steps. The aromatic segments **5** and **6** are anticipated to be prepared from commercially available methyl 3,5-dihydroxybenzoate (**7**) and 5-methylresorcinol (**8**), respectively.



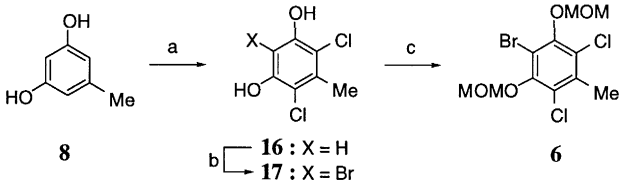
Scheme 2. Synthetic plan for (±)-geodin [(±)-**2**]

At first, we pursued the synthesis of the aryl aldehyde **5** starting from methyl 3,5-dihydroxybenzoate (**7**) as shown in Scheme 3. Thus, the known benzyl alcohol **10**, prepared from **7** according to the reported procedure,[10] was transformed to the benzyl ether **12** (88%, two steps) by regiospecific monobromination using 1.0 equiv. of *N*-bromosuccinimide (NBS) followed by benzylation of the resulting benzyl alcohol **11**. For introducing a formyl group, the aryl lithium generated in situ from **12** was allowed to react with *N*,*N*-dimethylformamide (DMF) to afford the 1,2,3,5-tetrasubstituted aryl aldehyde **13** in 81% yield. Direct conversion of **13** to the methoxymethyl (MOM) ether **15** by selective deprotection met with failure. Therefore, **13** was first converted to the resorcinol **14** by complete deprotection of the two MOM protecting groups, which was then subjected to selective monoprotection[11] [MOMCl (1.0 equiv.), K_2CO_3 (1.1 equiv.)], giving rise to **15** in 68% yield for the two steps. Finally, methylation of the remaining hydroxy group in **15** led to the requisite aryl aldehyde **5** in 90% yield.

Next, the aryl bromide **6**, the coupling partner of **5**, was synthesized from 5-methylresorcinol (**8**) via a three-step sequence of reactions (Scheme 4). Thus, bromination of the known dichlororesorcinol **16**,[12] prepared from **8** by reaction with sulfuryl chloride (2.5 equiv.) (38%), followed by protection of the two hydroxy groups in the resulting resorcinol **17** as its bis(MOM ether) provided the desired aryl bromide **6** (96%, two steps).



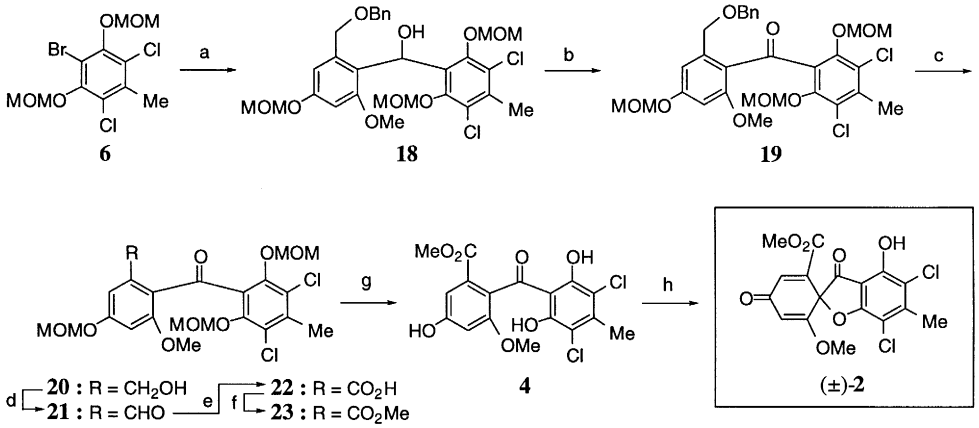
Scheme 3. Synthesis of the aryl aldehyde segment **5**. (a) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, rt, 87%; (b) $LiAlH_4$, Et_2O, rt, 98%; (c) NBS, DMF, 0°C, 93%; (d) BnBr, NaH, DMF, rt, 95%; (e) *n*-BuLi, Et_2O, −78°C; DMF, −78°C→rt, 81%; (f) 6 M HCl, THF, rt, 94%; (g) MOMCl, K_2CO_3, acetone, rt, 72%; (h) MeI, $CsCO_3$, DMF, rt, 90%



Scheme 4. Synthesis of the aryl bromide segment **6**. (a) SO_2Cl_2, $CHCl_3$, 0°C→rt, 38%; (b) Br_2, DMF, rt, 100%; (c) MOMCl, *i*-Pr_2EtN, CH_2Cl_2, 96%

Having obtained both the aryl aldehyde **5** and the aryl bromide **6**, our next efforts were devoted to completion of the synthesis of the targeted (±)-geodin [(±)-**2**] by assembling the two aromatic segments **5** and **6**. As shown in Scheme 5, the critical coupling reaction of **5** with the aryl lithium generated in situ from **6** proceeded smoothly, affording the desired coupling product **18** in 86% yield.[13] Subsequent oxidation of **18** by the use of Dess–Martin periodinane[14] provided the tetra-*ortho*-substituted benzophenone **19** in 95% yield. The benzophenone **19** was further converted to the methyl ester **23** (68%, four steps) via the benzyl alcohol **20**, the aldehyde **21**, and the carboxylic acid **22** by sequential debenzylation, two-step oxidation, and esterification. The three MOM protecting groups in **23** were completely removed by treatment with *p*-toluenesulfonic acid (*p*-TsOH) in refluxing methanol to provide the key cyclization precursor **4**[15] in 81% yield. After several experiments,[16] the crucial oxidative spirocyclization of **4** was found to be effected by treating **4** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[17] in dichloromethane-ethanol at ambient temperature, leading to the formation of (±)-**2**[18] in 57% yield. The ^1H NMR spectrum of the synthetic sample (±)-**2** was identical to that reported for (+)-(**2**).[9a]

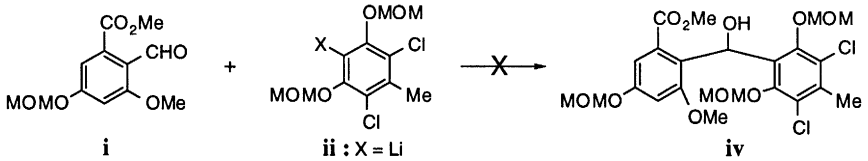
In summary, we have succeeded in developing a facile synthetic pathway to (±)-geodin [(±)-**2**] corresponding to the spirocoumaranone subunit of Sch 202596 (**1**) in a convergent manner starting from commercially available methyl 3,5-dihydroxybenzoate (**7**) and 5-methylresorcinol (**8**). The explored synthetic method features the coupling reaction of the aryl aldehyde **5** with the aryl bromide **6** and oxidative spirocyclization of the benzophenone **4**. Work on the total synthesis of **1** is in progress and will be reported shortly.



Scheme 5. Synthesis of (±)-geodin [(±)-**2**]. (a) *n*-BuLi, THF, −78°C; **5**, −78°C→rt, 86%; (b) Dess–Martin periodinane, CH_2Cl_2, rt, 98%; (c) H_2 (1 atm), 10% Pd–C, EtOH, rt, 79%; (d) Dess–Martin periodinane, CH_2Cl_2, rt, 95%; (e) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, THF–*tert*-BuOH–H_2O, rt; (f) CH_2N_2, Et_2O, 90% (two steps); (g) *p*-TsOH, MeOH, reflux, 81%; (h) DDQ, CH_2,Cl_2–EtOH, rt, 57%

References

1. Chu, M.; Mierzwa, R.; Truummes, I.; King, A.; Sapidou, E.; Barrabee, E.; Terracciano, J.; Patel, M. G.; Gullo, V. P.; Burrier, R.; Das, P. R.; Mittelmann, S.; Paur, M. S. *Tetrahedron Lett*. **1997**, *38*, 6111–6114.
2. It is noteworthy that Sch 202596 (**1**) is the only small molecule to date shown to inhibit [^{125}I]-galanin binding to GalR1-containing membranes prepared from human melanoma cells using a radioligand competition assay (IC_{50}=1.7 μM).[1]
3. So far, three galanin receptor subtypes, GalR1, GalR2, and GalR3, have been cloned and characterized. For a recent review on the galanin receptors as novel therapeutic targets, see: Wang, S.; Gustafson, E. L. *Drug News Perspect*. **1998**, *11*, 458–468.
4. (a) Crawley, J. N.; Robinson, J. K.; Langel, Ü.; Bartfai, T. *Brain Res*. **1993**, *600*, 268–272. (b) Rowland, N. E.; Kalra, S. P. *CNS Drugs* **1997**, 419–426. (c) Kask, K.; Berthold, M.; Bartfai, T. *Life Sci*. **1997**, *60*, 1523–1533.
5. Fathi, Z.; Church, W. B.; Lismaa, T. P. *Annu. Rep. Med. Chem*. **1998**, *33*, 41–50.
6. Structurally, **1** belongs to the griseofluvin family of compounds. Therefore, the absolute stereochemistry of the spirocoumaranone moiety in **1** was determined by comparing its circular dichroic (CD) spectrum with that of griseofluvin. The relative stereochemistry of the cyclohexene ring of **1** was revealed by analysis of 2D NMR spectra (COSY, NOESY, HETCOR, and HMBC experiments); however, its absolute stereochemistry has not been established.
7. Barton, D. H. R.; Scott, A. I. *J. Chem. Soc*. **1958**, 1767–1772.
8. Related biogenetic-type phenolic coupling reactions for the construction of the spirocoumaranone ring system have been reported, see: (a) Taub, D.; Kuo, C. H.; Slates, H. L.; Wendler, N. L. *Tetrahedron* **1963**, *19*, 1–17. (b) Day, A. C.; Nobney, J.; Scott, A. I. *J. Chem. Soc*. **1961**, 4067–4074. (c) Scott, A. I. *Proc. Chem. Soc*. **1958**, 195.
9. The biosynthetic pathway of (+)-geodin (**2**) has been well studied at the enzyme and molecular genetic level, see: (a) Huang, K.; Fujii, I.; Ebizuka, Y.; Gomi, K.; Sankawa, U. *J. Biol. Chem.* **1995**, *270*, 21495–21502. (b) Huang, K.; Yoshida, Y.; Mikawa, K.; Fujii, I.; Ebizuka, Y.; Sankawa, U. *Biol. Pharm. Bull*. **1996**, *19*, 42–46, and references cited therein.
10. (a) Srivastava, R. P.; Zhu, X.; Walker, L. A.; Sindelar, R. D. *Bioorg. Med. Chem. Lett*. **1995**, *5*, 2429–2434. (b) Hollinshead, S. P.; Nichols, J.; Wilson, J. W. *J. Org. Chem*. **1994**, *59*, 6703–6709. (c) Duffley, R. P.; Handrick, G. R.; Uliss, D. B.; Lambert, G.; Dalzell, H. G.; Razdan, R. K. *Synthesis* **1980**, 733–736.
11. In this reaction, reactivity of the hydroxy group adjacent to the formyl group in **14** would be precluded by the formation of an intramolecular hydrogen bond.
12. (a) Smith Jr, C. R. *J. Org. Chem*. **1960**, *25*, 588–591. (b) Natori, S. *Yakugaku Zasshi* **1951**, *71*, 371–373.
13. When the aryl aldehyde **i** (prepared from **7** by sequential formylation, selective MOM protection, and *O*-methylation) was used as a substrate for the coupling reaction with the aryl lithium **ii** (prepared in situ from **6**), none of the desired coupling product **iv** was obtained and the starting material **i** and the protonation product **iii** were recovered. This unsuccessful result might be attributable to the very low electrophilicity of the formyl group and/or steric hindrance of the methoxycarbonyl group in **i**.



i **ii : X = Li** **iii : X = H** **iv**

14. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem*. **1983**, *48*, 4155–4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc*. **1991**, *113*, 7277–7287. (c) Ireland, R. E.; Liu, L. *J. Org. Chem*. **1993**, *58*, 2899.
15. Compound **4**: Pale yellow prisms; mp 215.5–218°C; IR (KBr): 3420, 3213, 2920, 1725, 1647, 1541, 1400, 1261, 1097 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ: 2.48 (3H, s), 3.70 (3H, s), 3.71 (3H, s), 6.69 (1H, d, *J*=2.1 Hz), 7.00 (1H, d, *J*=2.1 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ: 200.7, 166.3, 158.6, 157.1, 155.4, 141.6, 128.4, 126.1, 112.2, 110.9, 107.5, 102.9, 55.1, 51.2, 17.5; EIMS *m/z*: 402 $[(M+2)^+]$, 400 (M^+), 370, 368, 341, 339, 337, 220, 218, 209, 183, 151.
16. When the phenol **4** was treated with a hypervalent iodine reagent, phenyliodine(III) bis(trifluoroacetate), in acetonitrile at ambient temperature according to the method reported by Kita et al., the desired spirocyclization product **2** could also be produced in 40% yield. See: (a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem*. **1987**, *52*, 3927–3930. (b) Kita, Y.; Egi, M.; Takada, T.; Tohma, H. *Synthesis* **1999**, 885–897.
17. Büchi, G.; Chu, P.-S.; Hoppmann, A.; Mak, C.-P.; Pearce, A. *J. Org. Chem*. **1978**, *43*, 3983–3985.
18. Compound (±)-**2**: Pale yellow amorphous powder; mp 247–249°C; IR (KBr): 3434, 2924, 1720, 1655, 1610, 1522, 1458, 1335, 1233 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): 2.58 (3H, s), 3.70 (3H, s), 3.75 (3H, s), 5.36 (1H, br s), 5.82 (1H, s), 7.15 (1H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 188.97, 185.04, 170.07, 165.91, 163.63, 163.08, 141.60, 139.12, 135.60, 119.55, 118.42, 108.02, 103.58, 84.58, 57.34, 52.81, 18.58. EIMS *m/z*: 400 $[(M+2)^+]$, 398 (M^+), 368, 366, 341, 339, 327, 325, 313, 298, 296, 209.