Concise Syntheses of Violaceoids A and C

Koichi Narita,*a Ryuhei Kimura,ª Hiroka Satoh,ª Kazuhiro Watanabe,*ª and Yuichi Yoshimuraa,b

ªLaboratory of Synthetic and Medicinal Chemistry, Faculty of Pharmaceutical Sciences, Tohoku Medical and Pharmaceutical University; 4–4–1 Komatsushima, Aoba-ku, Sendai 981–8558, Japan: and b Laboratory of Organic and Pharmaceutical Chemistry, Faculty of Pharmaceutical Sciences, Tohoku Medical and Pharmaceutical University; 4–4–1 Komatsushima, Aoba-ku, Sendai 981–8558, Japan.

Received October 8, 2020; accepted November 6, 2020; advance publication released online November 26, 2020

The concise syntheses of two alkyalted hydroquinone natural products, violaceoids A and C, were accomplished by a protecting-group-free method employing the commercially available 2,5-dihydroxybenzaldehyde as the starting material. The key strategy of the syntheses is the utilization of alkenyboronic acid as both the coupling and temporary protective reagents to efficiently introduce the requisite alkenyl side chain of violaceoid A. Moreover, the synthesis of violaceoid C is reported here for the first time.

Key words violaceoid; alkyalted hydroquinone; protecting-group-free synthesis; total synthesis

Introduction

In 2014, Sugawara and colleagues reported the isolation and structural elucidation of a new class of cytotoxic hydroquinones, violaceoids A–F (1–6, Fig. 1), from the culture broth of Aspergillus violaceofuscus Gasperini that was isolated from moss.1) Structurally, violaceoids possess a hydroxymethyl group and a linear alkyl side chain on the same side of the hydroquinone moiety. Although a similar structural feature was observed in the structures of frustulosinol2,3) and aspergentin,4) this substitution pattern is rare among disubstituted hydroquinones isolated from natural sources.5,6) Sugawara and colleagues also reported the cytotoxic activities of violaceoids against five human cancer cell lines (HeLa, MCF-7, Jurkat, MOLT-4, and HCT116) and a mouse macrophage cell line (RAW264.7). Among the violaceoids, violaceoid A (1), which possesses an unsaturated side chain, exhibited the most potent cytotoxic activity against all the six cell lines. Conversely, violaceoids B–D (2–4), which do not possess the olefin moiety on their side chains, exhibited weaker cytotoxic activities than those of 1. Therefore, it was suspected that the presence of a conjugated double bond in hydroquinone was essential for cytotoxicity. The first total syntheses of 1 and 2 were performed by Shiina and colleagues in 2018, and the absolute configuration of 2 was established by its synthesis.7) They utilized 3,6-dihydroxyphthalonitrile as a starting material, and the synthetic route required a relative multistep sequence involving protection–deprotection and oxidation–reduction steps (1: 10 steps, 11% overall yield; 2: 21 steps, including several repetitive kinetic resolutions and acetonide deprotection steps and 1.3% overall yield). In this study, we observed that boronic acid played a dual role, as a protective and coupling reagent, in the Suzuki–Miyaura cross-coupling of 3-bromo-2-(hydroxymethyl)phenol, and a concise synthesis of 1 employing this strategy was described. Furthermore, the conversion of 1 into 3 was also described.

Results and Discussion

Our retrosynthetic analyses of 1 and 3 are outlined in Chart 1. We envisaged that the alkenyl side chain of 1 could be introduced via the Suzuki–Miyaura cross-coupling reaction of aryl bromide 8 with the known alkenylboronic acid 9.8) Subsequently, a deprotection reaction of the coupling product 7 would afford 1. We also anticipated that the acid-labile protecting groups of 7 (i.e., the acetone and methoxymethyl (MOM) groups) would be simultaneously removed under an acidic condition, which would also reduce the number of reaction steps. Additionally, the reduction of the alkenyl side chain of 1 would afford 3.

Initially, we attempted the synthesis of 8, which is a substrate for the Suzuki–Miyaura cross-coupling with the commercially available 2,5-dihydroxybenzaldehyde (10) as the starting material (Chart 2). Phenol 13 was prepared from 10 in three steps according to a known procedure 9,10) (regioselective bromination,11) reduction, and acetonide protection). The protection of the phenolic hydroxyl group of 13 afforded 8 with a yield of 94%.

Next, we examined the Suzuki–Miyaura cross-coupling reaction of 8 with 9 (Chart 3). The coupling reaction proceeded smoothly employing 1.5 equivalent (equiv.) of 9, 3.0 equiv. of tert-butylamine, and 4 mol% PdCl2(dppf)·CHCl3 in i-PrOH/H2O at 100°C for 20 h, thereby affording the desired

Fig. 1. Structures of Violaceoids A–F (1–6)
Having successfully introduced the alkenyl side chain, we focused on the one-pot deprotection of acetonide and the MOM group of 7 to complete the synthesis of 1. The intermediate 7 was subjected to 3 M HCl in different solvents, such as MeOH, EtOH, tetrahydrofuran (THF), and acetone. However, 1 was not obtained in all the solvents. From these results, it was evident that the clean and efficient simultaneous deprotections of acetonide and the MOM group of 7 under acidic conditions were difficult. Therefore, we revised our synthetic route.

Our 2nd synthetic plan is outlined in Chart 4. Boronate esters are well-known as the protective groups of diols. Thus, we envisaged that the 1,3-diol moiety of 12 could be protected by a boronate ester by esterification with 9 employing the Suzuki–Miyaura cross-coupling reaction. Furthermore, an alkenyl boronate ester would be obtained from 14 via the Suzuki–Miyaura cross-coupling with another boronic acid 9 in the same pot. Finally, the hydrolysis of 15 afforded 1. Several examples of the protecting-group-free Suzuki–Miyaura cross-coupling of 1-bromo-2,5-hydroquinone have been reported in literature but the reaction of hydroquinone 12 which contains a 1,3-diol unit, has not been reported. We believed that these one-pot sequential reactions focused on the 1,3-diol unit in 12 enabled the protecting-group-free synthesis of 1.

In literature, 12 was reported only as a synthetic intermediate of 13, and a crude product of 12 was utilized for the next step, as shown in Chart 2. Thus, the isolation and characterization of 12 have not been reported. Hence, we examined the isolation and purification of the crude compound of 12 (Chart 5). After the reduction of the aldehyde 11 the crude material was purified by silica gel column chromatography and a pure compound 12 was obtained in 86% yield without any complication, such as the air oxidation of hydroquinone. Next, we investigated the one-pot protection/Suzuki–Miyaura cross-coupling of 12 with 9 under the same condition as aforementioned (1.5 equiv. of 9, 3.0 equiv. of tert-butylamine, i-PrOH/H2O, 100 °C, 4 h, 86%; and (c) H2 (1 atm), 10% Pd/C, EtOAc, r.t., 2 h, 87%).

Reagents and conditions: (a) PdCl2(dppf)-CH2Cl2, tert-butylamine, i-PrOH/H2O, 100 °C, 20 h, 84%. dppf = 1,1-bis(diphenylphosphino)ferrocene.

Chart 3. Attempted Synthesis of 1

Chart 4. Revised Synthetic Plan for 1

Chart 5. Syntheses of 1 and 3

Chart 1. Synthetic Plans for 1 and 3

Chart 2. Synthesis of 8

Chart 4. Revised Synthetic Plan for 1
converted into 14 as a protected form of the 1,3-diol unit in 12 by 9. Resultantly, the stability of 12 was improved. Next, the Suzuki–Miyaura cross-coupling of 14 with another 9 proceeded to afford the coupling product 15. The boronate ester moiety of 15 was gradually hydrolyzed, resulting in the formation of 1. Furthermore, we expected that boric acid, which was generated in the reaction, contributed to the improved stability of 1, i.e., the ester 16 which was generated in situ via the esterification of 1 with boric acid, suppressed the degradation of 1. Finally, the acidic workup of 16 afforded 1. Although all the steps were reversible reactions except for the Suzuki–Miyaura cross-coupling, we suspected that these steps with the formation of the boronate ester enabled the efficient synthesis of 1 from 12. To the best of our knowledge, this is the first report on the utilization of alkenylboronic acid as a coupling reagent and a temporary protective one.

Conclusion

We achieved the concise syntheses of 1 and 3 employing the commercially available 2,5-dihydroxybenzaldehyde (10) as the starting material: 1 (69% overall yield in three steps; 3: 60% overall yield in four steps). The total synthesis of 3 was reported here for the first time. The key step of the synthesis was the one-pot protection/Suzuki–Miyaura cross-coupling of 12 utilizing 9. This reaction enabled the protecting-group-free and concise synthesis of 1, achieving the gram-scale synthesis of 1. Further studies are ongoing to synthesize the analogs of violaceoids possessing various alkenyl or alkyl side chains to explore their structure–activity relationships.

Acknowledgments

This study was financially supported by a Japan Society for the Promotion of Science (JSPS) KAKENHI (Grant Number JP 20K15960 to K.N., 19K08663 and 16K08663 to K.W.).

Conflict of Interest

The authors declare no conflict of interest.

Supplementary Materials

The online version of this article contains supplementary materials.

References and Notes

1) Myobatake Y., Takemoto K., Kamisuki S., Inoue N., Takasaki A., Takeuchi T., Mizushima Y., Sugawara F., J. Nat. Prod., 77, 1236–1240 (2014).
2) Dubin G.-M., Fkyerat A., Tabacchi R., Phytochemistry, 53, 571–574 (2000).
3) Nair M. S. R., Anchel M., Phytochemistry, 16, 390–392 (1977).
4) Sun S.-W., Li C.-Z., Gu Q.-Q., Li D.-H., Zhu T.-J., J. Asian Nat. Prod. Res., 15, 956–961 (2013).
5) García P. A., Hernández A. P., Feliciano A. S., Castro M. Á., Mar. Drugs, 16, 292 (2018).
6) Sunassee S. N., Davies-Coleman M. T., Nat. Prod. Rep., 29, 513–535 (2012).
7) Murata T., Kuboki T., Ishikawa R., Saito T., Taguchi S., Takeuchi K., Hatano E., Shimonaka M., Shiina I., J. Nat. Prod., 81, 2364–2370 (2018).
8) Kobayashi Y., Nakayama Y., Mizoiri R., Tetrahedron, 54, 1053–1062 (1998).
9) Carr J. L., Offermann D. A., Holdom M. D., Dusart P., White A. J., P., Beavil A. J., Leatherbarrow R. J., Lindell S. D., Sutton B. J., Spivey A. C., Chem. Commun., 46, 1824–1826 (2010).
When MeOH or EtOH was used as a solvent, substitution reaction of hydroxy group at hydroxymethyl moiety by alcohol was observed, and alkoxylated violaceoid A was obtained (76% for O-methylated product or 24% for O-ethylated product). When acetone or THF was used as a solvent, the reaction became complicated and complex mixture was obtained. Although we could not isolate ester 16, the stability of violaceoid A (1) was improved in the presence of boric acid. When violaceoid A (1) was treated with 1.5 equiv. of boric acid and 3.0 equiv. of tert-butylamine in i-PrOH/H2O at 100°C for 2 h, 82% of 1 was recovered.