HETEROCYCLES, Vol. 102, No. 8, 2021, pp. 1570 - 1578. © 2021 The Japan Institute of Heterocyclic Chemistry
Received, 22nd April, 2021, Accepted, 12th May, 2021, Published online, 14th May, 2021
DOI: 10.3987/COM-21-14480

TOTAL SYNTHESIS OF HYALODENDRIOL C

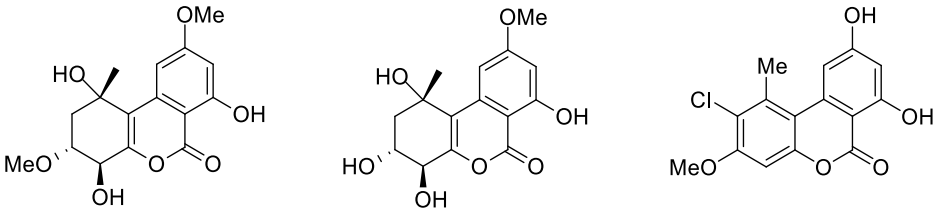
Ishtiaq Jeelani,[a]* Katsunori Itaya,[b] and Hitoshi Abe[b]

a) Graduate School of Innovative Life Science, University of Toyama, 3190 Gofuku 930-8555, Japan, b) Faculty of Engineering, University of Toyama, 3190 Gofuku, Toyama 930-8555, Japan. E-mail: ishtiaqjeelani66@gmail.com

Abstract – We present a total synthesis of hyalodendriol C, a fungal natural product. We have focused on the use of palladium-catalyzed intramolecular biaryl coupling reaction of phenyl benzoate derivatives to synthesize hyalodendriol C. Keeping in view, the indispensable biological values of this compound, we took the advantage of our established strategy to chemically synthesize hyalodendriol C. The total synthesis of hyalodendriol C got accomplished in 10 steps beginning with the preparation of phenol derivative from the commercially available 5-methylbenzene-1,3-diol and synthesis of the corresponding benzoic acid derivative.

Hyalodendriol C[1] as indicated in Figure **1**, chemically named as (2-chloro-7,9-dihydroxy-3-methoxy-1-methyl-6*H*-dibenzo[*b,d*]pyran-6-one), is a naturally occurring dibenzo-α-pyrones[2] and possesses a fused tricyclic nucleus. In 2016, Zhou and co-workers reported the isolation and structural elucidation of hyalodendriols A-C from endophytic fungus associated with the hybrid 'Neva of *Populus deltoides' x P. nigra* L.[1] A variety of biological activities have been stated for hyalodendriols A-C, but only hyalodendriol C has shown strong antibacterial, larvicidal, and antifungal properties as mentioned previously in the literature.[1] Particularly, it has shown strong antifungal effects with a value of IC_{50} of 11.6 µg mL^{-1} in opposition to the spore germination of *Magnaporthe oryzae*. It has also exhibited strong larvicidal activities in the case of the yellow fever mosquito that is known to spread severe diseases like Zika fever, dengue fever, chikungunya, and many other health problems. Conversely, hyalodendriols A and B which do not possess chloro substituents, exhibited weaker activities. Several natural products that possess 6*H*-dibenzo[*b,d*]pyran-6-one moiety are found to exhibit numerous biological activities.[3] Among the varied biological activities of these compounds, the most exciting bioactivity is anti-cancer activity against the SW1116 cell lines. The interesting structural feature of this compound is the aromatic ring

bearing chlorine atom. Natural products comprising a halogen on an olefinic, aromatic, heteroaromatic moieties as a substituent have gained considerable interest because of their multiple biological activities. Chlorine is one of the most requisite halogens and it has been well studied in medicinal chemistry as an important constituent in drugs to cure diverse illnesses such as meningitis, cholera, typhoid plague, fungal infections, bacterial skin infections, respiratory and neural complications.[4] Therefore, it was suspected that the presence of a chlorine atom was essential for the cytotoxicity of hyalodendriol C. We have focused on the synthesis of hyalodendriol C by making use of Pd-catalyzed biaryl coupling reaction of phenyl benzoate derivative for making 6*H*-dibenzo[*b*,*d*]pyran-6-one ring system. Since the Pd-catalyzed coupling reaction for such compounds was successful as our group has already described, we took advantage and planned the total synthesis of hyalodendriol C. The Pd-catalyzed biaryl coupling reaction is one of the most convenient techniques for the formation of carbon-carbon bonds between two aromatic rings among the various provisions of this kind of ring system. The intramolecular biaryl coupling reaction of phenyl benzoate derivatives using the Pd reagent has been documented to be widely useful for synthesizing several of these types of natural products.



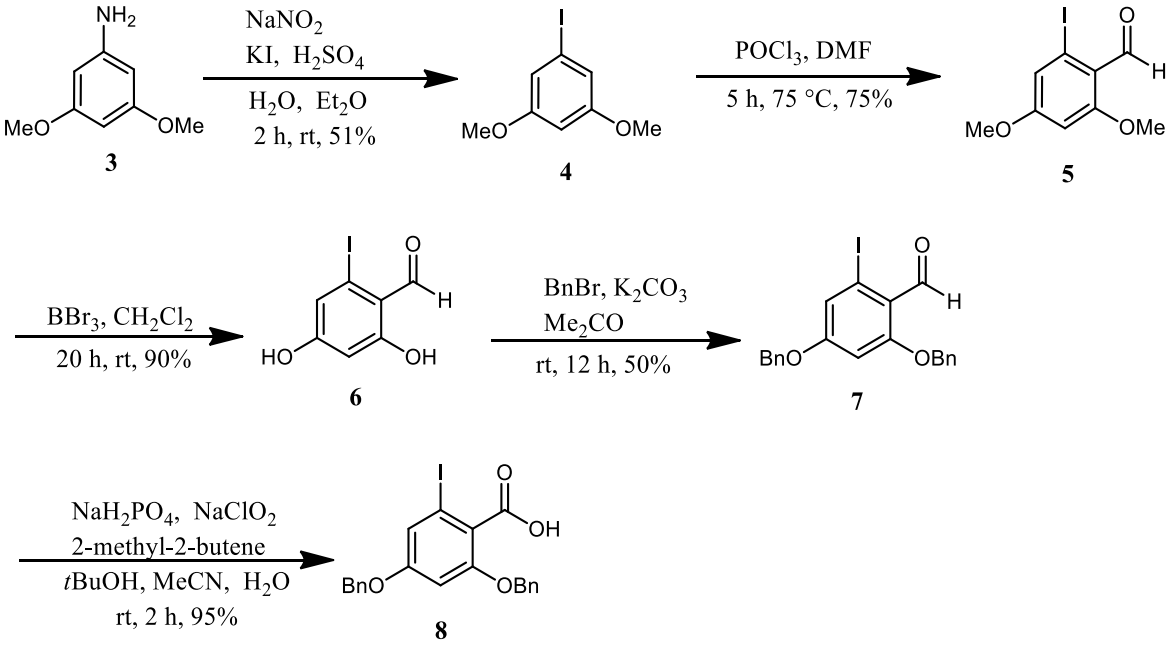
hyalodendriol A hyalodendriol B hyalodendriol C (**1**)

Figure 1. Structures of hyalodendriols A-C

The synthetic investigation of hyalodendriol C (**1**) started with the preparation of 4-chloro-5-methylbenzene-1,3-diol (**2**) by the known method, as an essential part of phenyl benzoate. Regioselective chlorination of commercially available orcinol to **2** using *N*-chlorosuccinimide (NCS), was carried out according to the literature.[5]

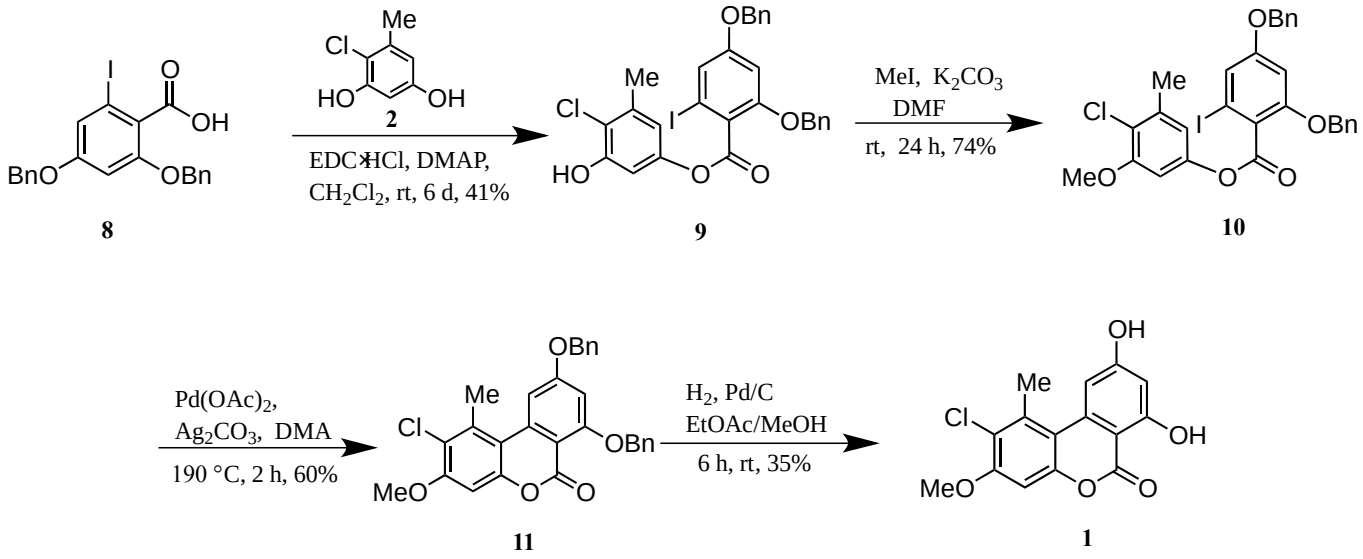
On the other hand, through 5 step transformations, the corresponding benzoic acid was prepared. First, commercially available 3,5-dimethoxyaniline (**3**) was iodinated to compound **4** with the substitution of the amino group into iodide via Sandmeyer reaction in presence of potassium iodide,[6] which was eventually subjected to Vilsmeyer conditions for the introduction of formyl group to produce compound **5**.[7] Then demethylation using BBr_3 was carried out to obtain compound **6**.[8] The dihydroxy group of compound **6** must be tentatively protected by the benzyl group using benzyl bromide to yield compound

7[8,9] before it was allowed for Pinnick oxidation to obtain the corresponding benzoic acid **8** (Scheme **1**). Compounds **2** and **8** have been prepared as per the reported methods and results were found to be matching including the spectroscopic data *e.g.*, ^{1}H-NMR, ^{13}C-NMR, Mass (HRMS (EI) *m/z*), and IR.



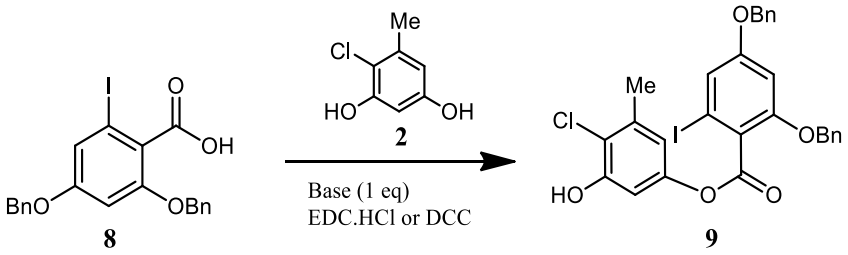
Scheme 1. Preparation of benzoic acid derivative

Esterification between **8** and **2** by using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl) and 4-dimethylaminopyridine (DMAP) as a base was successful to yield the key precursor **9**[10] in a moderate yield for the palladium-mediated biaryl coupling reaction[11] (Scheme **2**). Despite several attempts, the low yield continued to remain a concern, but almost 41% yield was observed via entry 6 when 2 equivalents phenol was used and the reaction was performed at rt for 6 days (Table **1**). The low yield of **9** may be due to condensation at both hydroxy groups. Compound **10** was successfully obtained from compound **9** using MeI and K_2CO_3 as a base[12] and this step was pleasingly found to offer a 74% yield. Then all-important intramolecular biaryl coupling reaction using Pd reagent was a significant potential for application to the construction of compound **11**. We examined the intramolecular biaryl coupling reaction using $Pd(OAc)_2$ and NaOAc as a base, in DMF at 150 °C with PPh_3 ligand which produced **11** in 56% yield. In the second run, Ag_2CO_3 was used as a base with PPh_3 but produced **11** in a low yield. A combination of $Pd(OAc)_2$ and NaOAc, with or without phosphine ligand produced the product in almost the same yield. However, $Pd(OAc)_2$ in presence of Ag_2CO_3 at 190 °C resulted in a 60% yield. Finally, deprotection using 10% Pd/C in presence of H_2[13] produced hyalodendriol C (**1**) successfully.



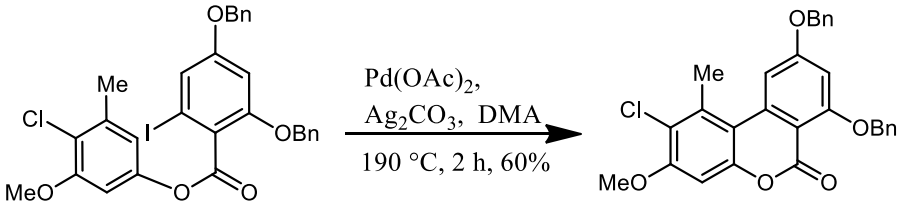
Scheme 2. Synthesis of hyalodendriol C (**1**)

Table 1. Reaction conditions for the esterification between **8** and **2**



Entry	Reagent	Base	Solvent	Phenol eq.	Time	Yield % of **9**
1	EDC (3 eq)	DMAP	DCM	1.05	10 h	15
2	DCC (3 eq)	DMAP	DCM	1.05	24 h	20
3	DCC (3 eq)	DMAP	$CHCl_3$	0.8	24 h	trace
4	DCC (3 eq)	DMAP	DMF	1.5	5 d	25
5	EDC (2 eq)	Et_3N (5 eq)	DCM	1	5 d	trace
6	EDC (1.15 eq)	DMAP	DCM	2	6 d	41

Table 2. Palladium-catalyzed cyclization reaction of **10**



10 **11**

Run	Catalyst	Ligand	Base	Time (h)	Temp.	Yield (%) of **11**
1	$Pd(OAc)_2$	PPh_3	NaOAc	2	130	56
2	$Pd(OAc)_2$	PPh_3	Ag_2CO_3	20	reflux	29
3	$Pd(OAc)_2$	none	NaOAc	2	130	57
4	$Pd(PPh_3)_4$	none	NaOAc	5	130	32
5	$Pd(OAc)_2$	PPh_3	NaOAc	2	reflux	11
6	$Pd(OAc)_2$	none	Ag_2CO_3	2	190	60

In conclusion, we could achieve the first total synthesis of hyalodendriol C (**1**) where we planned to employ the palladium-catalyzed biaryl coupling reaction developed by us, previously. Substrate for the coupling reaction was prepared through the esterification between benzoic acid derivative and phenol derivative. We will continue our efforts to further boost the yield by improving the reaction and the operating condition in the future. We also plan on synthesizing other related compounds. This work is expected to be applicable to the synthesis of other 6*H*-dibenzo[*b*,*d*]pyran-6-one natural products.

EXPERIMENTAL

General: All reactions were executed under N_2 atmosphere. Reaction solvents were used after purification by the standard methods. Reaction progress was observed with the help of thin-layer chromatography by making use of silica gel (70 F_{254}) TLC plates and UV light as an agent for visualizing. Silica gel (particle size: 100−200 and 230−400 mesh). Melting points (mp) were obtained and are uncorrected using the Yanaco micro melting point apparatus. With the Shimadzu FTIR 8400 spectrophotometer, the IR spectra were acquired. The JOEL α-400 MHz instrument was utilized for obtaining ^{1}H- and ^{13}C-NMR spectra with the couplings being shown in Hertz and chemical shift being expressed as δ ppm. Silica gel column chromatography was accomplished using Wakogel 60N, 63~212 μm.

4-Chloro-1,3-dihydroxy-5-methylbenzene (2) and **2, 4-Dibenzyloxy-6-iodobenzoic acid (8)** were prepared by the reported procedures.

4-Chloro-3-hydroxy-5-methylphenyl 2, 4-dibenzyloxy-6-iodobenzoate (9)

To a 100-mL, two-necked, round-bottomed flask, equipped with a 1.0-cm, egg-shaped stir bar and fitted with nitrogen inlet, was charged with a solution of 2,4-dibenzyloxy-6-iodobenzoic acid **(8)** (500 mg, 1.087 mmol) in CH_2Cl_2 (16 mL) and stirring was begun to dissolve the solid. EDC·HCl (245 mg, 1.08 mmol), DMAP (65 mg, 0.54 mmol) and 4-chloro-1,3-dihydroxy-5-methylbenzene (**2**) (345 mg, 1.17 mmol) were added. The reaction mixture was stirred for 6 days at rt. A TLC analysis of the solution using (hexane/EtOAc/CH_2Cl_2, 3/1/0.25) showed the reaction was complete. The reaction mixture was then poured into water and then aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The organic layer was washed with saturated brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give a residue that was subjected to column chromatography (hexane/EtOAc/CH_2Cl_2, 3/1/0.25). White solid product was obtained (269 mg, 41%) yield, mp 162.9-164.2 °C; IR KBr/cm : 3384, 1732, 1589, 910, 762, 611; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41-7.35 (m, 10H), 7.08 (d, *J* = 7.3 Hz, 1H), 6.72 (d, *J* = 2.7 Hz, 1H), 6.62 (d, *J* = 2.3 Hz, 1H), 6.58 (d, *J* = 2.7 Hz, 1H), 5.66 (s, 1H), 5.08 (s, 2H), 5.04 (s, 2H), 2.31 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.9, 161.1, 157.3, 152.0, 149.6, 137.6, 135.9, 135.8, 128.8, 128.8, 128.5, 128.4, 127.7, 127.6, 122.9, 118.0, 116.8, 115.9, 107.5, 101.0, 92.8, 77.4, 77.1, 76.8, 70.9, 70.6, 20.3; HRMS (EI) *m/z* [M^+] calculated for $C_{28}H_{22}O_5ICl$ 600.0200, found 600.0247.

4-Chloro-3-methoxy-5-methylphenyl 2, 4-dibenzyloxy-6-iodobenzoate (10)

To a 100-mL, two-necked, round-bottomed flask, enabled with a 1.0-cm, egg-shaped stir bar and fitted with nitrogen inlet was charged with a solution of 4-chloro-3-hydroxy-5-methylphenyl 2,4-dibenzyloxy-6-iodobenzoate **(9)** (240 mg, 0.39 mmol) in DMF (2.4 mL) and stirring was begun to dissolve the solid. K_2CO_3 (82 mg, 0.60 mmol) and MeI (0.025 mL) were added to the reaction mixture. A TLC analysis of the solution using EtOAc:hexane (1:3) specified the reaction was complete. After 24 h of stirring at rt, the reaction mixture was poured into water accompanied by layer separation. The aqueous layer was extracted with EtOAc (3×30 mL) whereas, the washing of the combined organic layer was done with additional water (3×20 mL) and one time with sodium chloride solution, dried over anhydrous $MgSO_4$, and evaporated to give a residue. Two times recrystallization from EtOAc yielded white coloured solid product (180 mg, 74%), mp 94.4-95.5 °C; IR KBr/cm :1745, 1696, 831, 736; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.43-7.35 (m, 10H), 7.09 (d, *J* = 1.8 Hz, 1H), 6.65 (d, *J* = 5.5 Hz, 2H), 6.53 (s, 1H), 5.06 (d, *J* = 2.3 Hz, 4H), 3.72 (s, 3H), 2.33 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.0, 161.1, 157.3, 155.6, 149.3, 138.4, 135.8, 128.9, 128.7, 128.5, 128.4, 127.8, 127.7, 122.9, 120.1, 116.8, 115.8, 103.7, 101.0, 92.8, 77.4,

77.1, 76.8, 71.0, 70.7, 56.3, 20.5; HRMS (EI) *m/z* [M^+] calculated for $C_{29}H_{24}O_5ICl$ 614.0399, found 614.0357.

2-Chloro-7,9-dibenzyloxy-3-methoxy-1-methyl-6*H*-dibenzo[*b,d*]pyran-6-one (11)

To a 100-mL, three-necked, round-bottomed flask, enabled with a 1.0-cm, egg-shaped stir bar and fitted with an extra funnel and a condenser (nitrogen inlet) was charged with a solution of 4-chloro-3-methoxy-5-methylphenyl 2,4-dibenzyloxy-6-iodobenzoate **(10)** (154 mg, 0.24 mmol) in DMA (3 mL), $Pd(OAc)_2$ (5.60 mg, 0.46 mmol) and Ag_2CO_3 (138.09 mg, 0.50 mmol) were added. The reaction mixture was then stirred for 5 min at rt and subsequently heated at 190 °C for 2 h. Later, at room temperature, the reaction mixture was cooled down, diluted with EtOAc, filtered to remove undissolved materials and then the filtrate was poured into 10 mL water and extracted with EtOAc (3×20 mL). The organic layer was washed with water and sodium chloride solution, dried over anhydrous $MgSO_4$ and evaporated to give a brown mixture. Column chromatography (hexane/EtOAc, 3/1) was employed to yield **11** as white powder (74 mg, 60%), mp 187.1-188.3 °C; IR KBr/cm : 1720, 1600, 823, 734; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 6.9 Hz, 2H), 7.44-7.36 (m, 8H),7.14 (d, *J* = 1.8 Hz, 1H), 6.76 (s, 1H), 6.67 (d, *J* = 1.8 Hz, 1H), 5.29 (s, 2H), 5.17 (s, 2H), 3.94 (s, 3H), 2.70 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 163.5, 162.6, 157.3, 156.1, 151.7, 139.7, 136.3, 135.8, 134.9, 128.9, 128.7, 128.5, 127.9, 127.4, 126.8, 120.6, 112.4, 104.8, 104.6, 100.4, 98.4, 77.4, 77.1, 76.8, 71.0, 70.5, 56.5, 21.2; HRMS (EI) *m/z* [M^+] calculated for $C_{29}H_{23}O_5Cl$ 486.1261, found 486.1234.

Hyalodendriol C (2-Chloro-7,9-dihydroxy-3-methoxy-1-methyl-6*H*-dibenzo[*b,d*]pyran-6-one) (1)

To a 25-mL, two-necked, round-bottomed flask, enabled with a 0.5-cm, egg-shaped stir bar and fitted with a hydrogen inlet was charged with a solution of 2-chloro-7,9-dibenzyloxy-3-methoxy-1-methyl-6*H*-dibenzo[*b,d*]pyran-6-one **(11)** (42 mg, 0.086 mmol) in 1:1 MeOH/EtOAc (1 mL) followed by the addition of 10% Pd/C (52 mg). The resulting mixture was stirred for 6 h at rt under H_2 atmosphere. A TLC analysis of the solution using EtOAc:hexane (1:2) indicated the reaction was complete, after which the mixture was filtrated to remove the catalyst and eluted with EtOAc. The volatiles were evaporated to provide the crude which was subjected to column chromatography (hexane/EtOAc, 2:1) to yield hyalodendriol C (**1**) as brown solid, (10 mg, 35%), mp 235-237 °C. IR KBr/cm :3284, 2850, 2362, 1652, 1580, 1490, 1410, 1350, 1220, 1070, 983, 760, 720; ^{1}H-NMR (400 MHz, DMSOd_6) δ 7.21 (d, *J* = 1.8 Hz, 1H), 7.16 (s, 1H), 6.42 (d, *J* = 1.8 Hz, 1H), 3.94 (s, 3H), 2.81 (s, 3H); ^{13}C-NMR (100 MHz, DMSOd_6) δ 163.9, 150, 132.2, 129.2, 67.9, 40.6, 40.4, 40.2, 40.0, 39.8, 39.6, 39.4, 38.6, 30.3, 29.5, 28.9, 22.9; HRMS (EI) *m/z* [M^+] calcd for $C_{15}H_{11}O_5Cl$ 306.0253, found 306.0295.

ACKNOWLEDGEMENTS

A part of this study was financially supported by THE HOKURIKU BANK Grant-in-aid for young scientists for H.A.

REFERENCES

1. Z. Mao, D. Lai, X. Liu, X. Fu, J. Meng, A. Wang, X. Wang, W. Sun, Z. L. Liu, L. Zhou, and Y. Liu, *Pest Manag. Sci.*, 2017, **73**, 1478.
2. Z. Mao, W. Sun, L. Fu, H. Luo, D. Lai, and L. Zhou, *Molecules*, 2014, **19**, 5088.
3. (a) B. I. Alo, A. Kandil, P. A. Patil, M. J. Sharp, M. A. Siddiqui, V. Snieckus, and P. D. Josephy, *J. Org. Chem.*, 1991, **56**, 3763; (b) Y. C. Song, W. Y. Huang, C. Sun, F. W. Wang, and R. X. Tan, *Biol. Pharm. Bull.*, 2005, **28**, 506; (c) T. Tanahashi, M. Kuroishi, A. Kuwahara, N. Nagakura, and N. Hamada, *Chem. Pharm. Bull.*, 1997, **45**, 1183.
4. (a) W.-Y. Fang, L. Ravindar, K. P. Rakesh, H. M. Manukumar, C. S. Shantharam, N. S. Alharbi, and H.-L. Qin, *Eur. J. Med. Chem.*, 2019, **173**, 117; (b) J. Tian, X. C. Liu, Z. L. Liu, D. Lai, and L. Zhou, *Pest Manag. Sci.*, 2016, **72**, 961.
5. K. Mori and K. Sato, *Tetrahedron*, 1982, **38**, 1221.
6. (a) W.-w. Mao, T.-t. Wang, H.-p. Zeng, Z.-y. Wang, J.-p. Chen, and J.-g. Shen, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 4570; (b) K. Tahara, H. Yamaga, E. Ghijsens, K. Inukai, J. Adisoejoso, M. O. Blunt, S. D. Feyter, and Y. Tobe, *Nat. Chem*., 2011, **3**, 714.
7. (a) H. Abe, T. Fukumoto, Y. Takeuchi, and T. Harayama, *Heterocycles*, 2007, **74**, 265; (b) K. Ahmed, S. Enumula, A. Pangal, I. Jeelani, M. Rane, G. Mahangade, and V. Patel, *Int. J. Pharm. Biol. Sci.*, 2019, **9**,1000.
8. (a) H. Mikula, P. Skrinjar, B. Sohr, D. Ellmer, C. Hametner, and J. Fröhlich, *Tetrahedron*, 2013, **69**, 10322; (b) M. Node, T. Kajimoto, K. Nishide, E. Fujita, and K. Fuji, *Bull. Inst. Chem. Res.*, *Kyoto Univ.*, 1992, **70**, 308.
9. M. Tanaka, Y. Ikeya, H. Mitsuhashi, M. Maruno, and T. Wakamatsu, *Tetrahedron*, 1995, **51**, 11703.
10. (a) H. Abe, T. Fukumoto, Y. Horino, T. Harayama, and Y. Takeuchi, *Heterocycles*, 2010, **82**, 851; (b) R. Frlan, S. Gobec, and D. Kikelj, *Tetrahedron*, 2007, **63**, 10698; (c) S. Balamurugan, P. Kannan, P. Yadupati, and A. Roy, *J. Mol. Struct*., 2011, **1001**, 118; (d) M. Kitamura, S. Takahashi, and T. Okauchi, *J. Org. Chem*., 2015, **80**, 8406; (e) C.-X. Su, J.-F. Mouscadet, C.-C. Chiang, H.-J. Tsai, and L.-Y. Hsu, *Chem. Pharm. Bull*., 2006, **54**, 682.
11. (a) T Harayama, H. Yasuda, T. Akiyama, Y. Takeuchi, and H. Abe, *Chem. Pharm. Bull*., 2000, **48**, 861; (b) S. Takeda, H. Abe, Y. Takeuchi, and T. Harayama, *Tetrahedron*, 2007, **63**, 396; (c) H. Abe, K. Nishioka, S. Takeda, M. Arai, Y. Takeuchi, and T. Harayama, *Tetrahedron Lett*., 2005, **46**, 3197; (d)

H. Abe, S. Takeda, T. Fujita, K. Nishioka, Y. Takeuchi, and T. Harayama, *Tetrahedron Lett*., 2004, **45**, 2327; (e) H. Abe, Y. Sahara, Y. Matsuzaki, Y. Takeuchi, and T. Harayama, *Tetrahedron Lett.*, 2008, **49**, 605; (f) H. Abe and T. Harayama, *Heterocycles*, 2008, **75**, 1305; (g) H. Abe, M. Arai, K. Nishioka, T. Kida, K. Shioe, Y. Takeuchi, and T. Harayama, *Heterocycles*, 2008, **76**, 291; (h) K. Shioe, Y. Takeuchi, T. Harayama, and H. Abe, *Chem. Pharm. Bull*., 2010, **58**, 435; (i) H. Abe, M. Arai, Y. Takeuchi, and T. Harayama, *Heterocycles*, 2009, **77**, 1409.

12. D. M. W. Anderson and G. M. Cree, *Carbohydr. Res.*, 1966, **2**, 162.
13. H. Miyazaki, N. Nakamura, T. Ito, T. Sada, T. Oshima, and H. Koike, *Chem. Pharm. Bull.*, 1989, **37**, 2379.