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Total synthesis of mallotophilippen C

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Abstract—The first total synthesis of mallotophilippen C (**1**), a bioactive chalcone natural product recently isolated from *Mallotus philippinensis* MUELL. ARG., is described. The synthesis has been accomplished in 11 linear steps from a commercially available material, with an overall yield of 28%.

Mallotus philippinensis MUELL. ARG. (Euphorbiaceae) is a deciduous tree widely distributed throughout tropical Asia, Australia and the Philippines. The granular hairs on the surface of its fruits are called kamala, and have long been used as both an anthelmintic and a cathartic in traditional medicine.[1]

Mallotophilippens C (**1**), D (**2**) and E (**3**) are three novel chalcone natural products (Fig. 1), first isolated by Daikonya et al.[2] from the fruits of the *Mallotus philippinensis* MUELL. ARG. They were shown to inhibit the production of nitric oxide (NO) induced by interferon-γ (IFN-γ) and lipopolysaccharide (LPS) in murine macrophage-like cell line, RAW 264.7. Furthermore, they also inhibit inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), interleukin-6 (IL-6) and interleukin-1β (IL-1β) mRNA expression. These results suggest that they have anti-inflammatory and immunoregulatory effects, and may be candidates for drugs to treat diseases due to iNOS over expression.

Mallotophilippen C (**1**) is an attractive target, exhibiting the best inhibitory activity ($IC_{50} = 3.6$ μg/ml) of the three chalcone natural products (**2**, $IC_{50} = 4.7$ μg/ml; **3**, $IC_{50} = 18.9$ μg/ml) against NO production, and exhibiting stronger inhibition activity than that of the positive control Quercetin[3] ($IC_{50} = 8.1$ μg/ml). As we were intrigued by the potent bioactivity of mallotophilippen C (**1**) and interested in the new structure, we began the synthetic study and achieved the first total synthesis of this novel chalcone natural product.

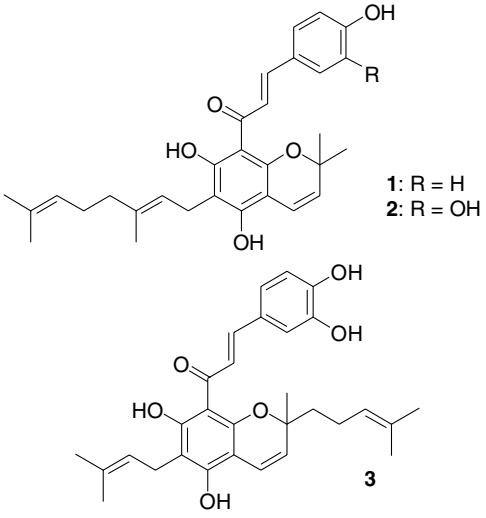

Figure 1. Structures of mallotophilippens C, D and E.

According to our retrosynthetic analysis (Scheme 1), mallotophilippen C (**1**) synthesis could be envisaged through the Claisen–Schmidt condensation of 4-methoxymethoxy-benzaldehyde with **13**, which could in turn be derived from **8** through directed *ortho* metalation (D*o*M) methodology to install the geranyl chain. Compound **8** could be converted from readily accessible phloroacetophenone (**4**).

Keywords: Inhibit NO production; Mallotophilippen C; Total synthesis.
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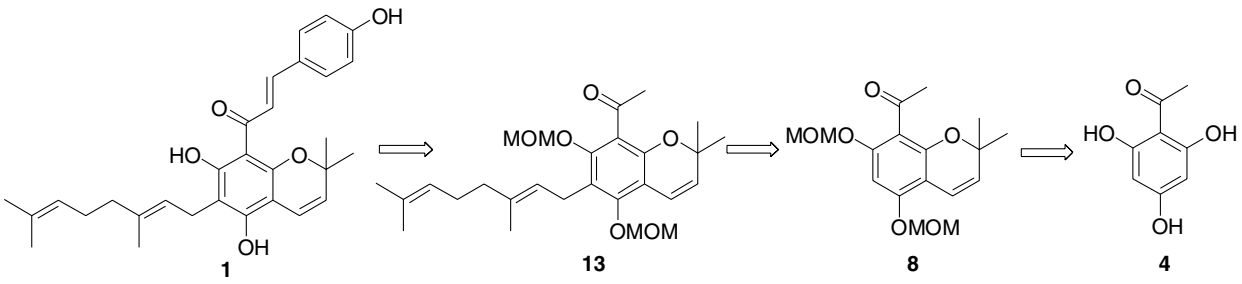
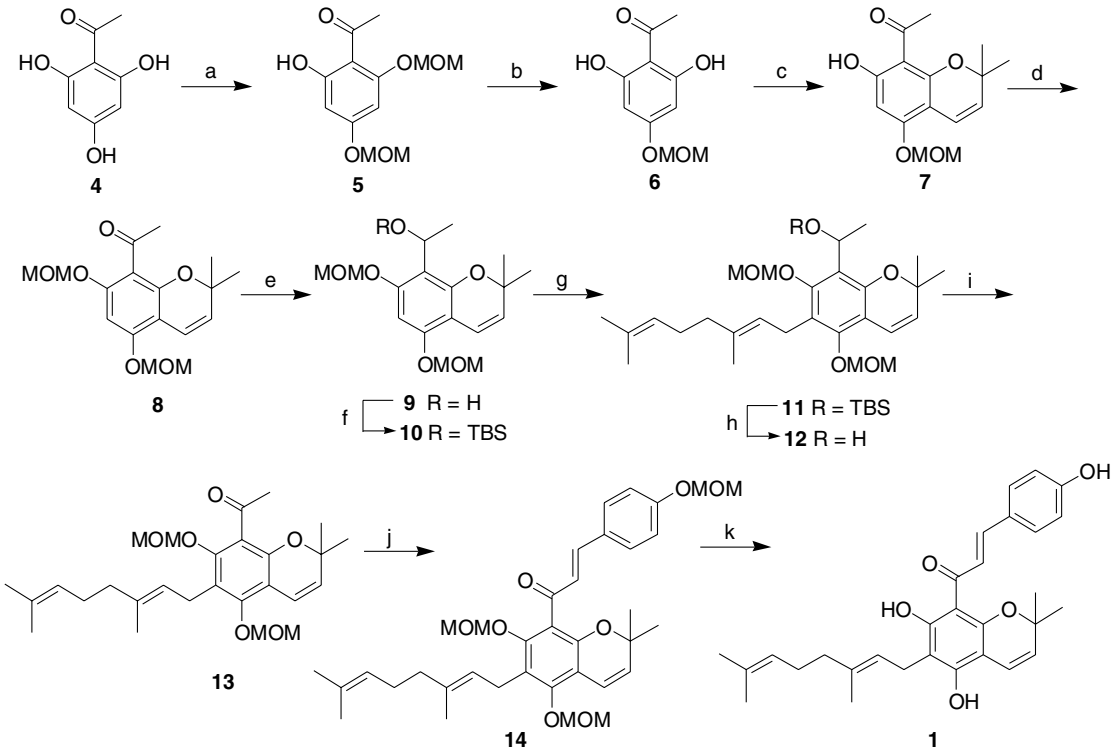


Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) MOMCl, DIPEA, CH_2Cl_2, 0 °C to rt, 1 h, 84%; (b) I_2 (1 wt/vol % I_2/MeOH), MeOH (0.1 M), rt, 16 h, 82%; (c) 3-methyl-2-butenal, pyridine, reflux, 16 h, 83%; (d) MOMCl, NaH, DMF, rt, 2 h; (e) $LiAlH_4$, THF, rt, 4 h; (f) TBSCl, imidazole, DMF, rt, 0.5 h, 95% (over three steps); (g) *n*-BuLi, TMEDA, CuCN, THF, −20 °C; geranyl bromide, THF, −78 °C, 12 h, 80%; (h) TBAF, THF, reflux, 3 h; (i) PDC, CH_2Cl_2, rt, 24 h, 93% (over two steps); (j) 4-methoxymethoxy-benzaldehyde, 55% KOH (230 equiv), EtOH, 0 °C to rt, 16 h, 87%; (k) 3 N HCl, MeOH, reflux, 25 min, 81%.

To initiate the sequence (shown in Scheme 2), phloroacetophenone (**4**) was protected with methoxymethyl chloride (MOMCl) to give **5**,[4] which was followed by selective cleavage of the *ortho*-MOM ether with iodine in methanol[5] to afford **6**[6] in 82% yield. Treatment of **6** with 3-methyl-2-butenal in refluxing pyridine[7] provided chromene **7** in 83% yield. Prolonging the reaction time led to the cleavage of *para*-MOM ether and octandrenolone[8] was obtained as a major byproduct.

We then focused on the introduction of the geranyl chain to the phenyl moiety. The strategy of directed *ortho* metalation (D*o*M),[9] which has been proved to be an efficient method to install a geranyl chain, was used to achieve this goal.

The free phenol of **7** was etherified with MOMCl and sodium hydride in DMF to afford acetophenone **8**, which was reduced by $LiAlH_4$ in THF to give the corresponding alcohol **9**. The two steps proceeded smoothly without the detection of any byproducts. After the protection of the alcoholic group of **9** with *tert*-butyldimethylsilyl chloride (TBSCl), the crude product was purified by flash column chromatography on silica gel to give **10** in 95% yield over three steps.

With the key intermediate **10** in hand, the next step required the introduction of the geranyl chain into the phenyl moiety. This compound was subjected to D*o*M conditions, followed by lithium–copper exchange and alkylation with geranyl bromide. The reaction proceeded slowly to afford the product **11** and a small quantity of the starting material **10**. After workup, the crude product was purified by column chromatography to obtain **11** in 80% yield, based on unrecovered **10** as a clear oil. Cleavage of the silyl ether **11** by tetrabutylammo-

nium fluoride (TBAF) in refluxing THF gave alcohol **12**. Compound **12** was oxidized with pyridinium dichromate (PDC) in CH_2Cl_2 to provide **13** after 24 h stirring at room temperature, in 93% yield over two steps.

Prior work has shown that the Claisen–Schmidt condensation[10] can be achieved with excess of KOH or NaOH in an alcoholic aqueous solution from 0 °C up to refluxing temperature. Condensation of acetophenone **13** with 4-methoxymethoxy-benzaldehyde[11] was accomplished in a mixture of aqueous KOH and ethanol at 0 °C to room temperature under nitrogen for 16 h. The 3MOM-protected chalcone **14** was thus obtained in 87% yield without the evidence of the undesired *cis* enone. Almost no product was detected when **13** was reacted with 4-hydroxy-benzaldehyde under the same condition after 24 h, although a similar reaction proceeded smoothly when **13** was replaced with 1-(2,4-bis-methoxymethoxy-phenyl)-ethanone.[12]

With the core chalcone framework established, the final step was to remove the protective groups to give the target material mallotophilippen C (**1**). All the MOM groups of **14** were removed by hydrolysis using 3 N HCl in methanol to afford **1** in 81% yield. Increasing the concentration of HCl or prolonging the reaction time led to a decrease in yield, due to the instability of **1** in acidic environment. The spectral data (shown in Supplementary data) of compound **1** were in agreement with that of the reference.[2]

In conclusion, an efficient first total synthesis of the bioactive natural product, mallotophilippen C (**1**), has been achieved. Starting from the readily accessible phloroacetophenone (**4**), a linear sequence of 11 steps allowed us to obtain **1** in 28% overall yield. The synthetic route outlined here, with steps of procedural simplicity and high efficiency, facilitates our further structural modification and biological studies of this kind of compounds.

Acknowledgements

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Supplementary data

Experimental data for compounds **1** and **6**–**14** are included. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.04.064.

References and notes

1. Satyavati, G. V.; Gupta, K. A.; Tandon, N. *Med. Plants India* **1987**, *2*, 201.
2. Daikonya, A.; Katsuki, S.; Kitanaka, S. *Chem. Pharm. Bull.* **2004**, *52*, 1326.
3. Manjeet, K. R.; Ghosh, B. *Int. J. Immunopharmacol.* **1999**, *21*, 435.
4. Kumazawa, T.; Minatogawa, T.; Matsuba, S.; Sato, S.; Onodera, J.-i. *Carbohydr. Res.* **2000**, *329*, 507.
5. Keith, J. M. *Tetrahedron Lett.* **2004**, *45*, 2739.
6. Tsujihara, K.; Hongu, M.; Saito, K.; Kawanishi, H.; Kuriyama, K.; Matsumoto, M.; Oku, A.; Ueta, K.; Tsuda, M.; Saito, A. *J. Med. Chem.* **1999**, *42*, 5311.
7. Thebtaranonth, C.; Imraporn, S.; Padungkul, N. *Phytochemistry* **1981**, *20*, 2305.
8. Pernin, R.; Muyard, F.; Bévalot, F.; Tillequin, F.; Vaquette, J. *J. Nat. Prod.* **2000**, *63*, 245.
9. (a) Treadwell, E. M.; Cermak, S. C.; Wiemer, D. F. *J. Org. Chem.* **1999**, *64*, 8718; (b) Neighbors, J. D.; Salnikova, M. S.; Wiemer, D. F. *Tetrahedron Lett.* **2005**, *46*, 1321.
10. (a) Ahmad, S.; Wagner, H. *Tetrahedron* **1978**, *34*, 1593; (b) Ali, S. M.; Ilyas, M. *J. Org. Chem.* **1986**, *51*, 5415; (c) Davis, F. A.; Chen, B.-C. *Tetrahedron Lett.* **1990**, *31*, 6823.
11. Lion, C. J.; Matthews, C. S.; Stevens, M. F. G.; Westwell, A. D. *J. Med. Chem.* **2005**, *48*, 1292.
12. Shimamura, T.; Arakawa, Y.; Hikita, K.; Niwa, M. *Heterocycles* **1996**, *43*, 2223.