ORGANIC LETTERS

2007
Vol. 9, No. 26
5369−5372

Total Synthesis of Munchiwarin, a Triprenylated Chalcone from *Crotalaria medicagenia*[#]

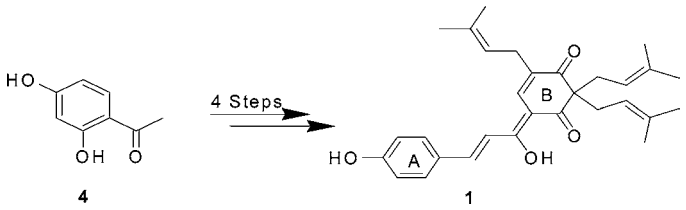
T. Narender,[*,§] K. Papi Reddy,[§,†] Shweta,[§,‡] Kumkum Srivastava,[⊥] D. K. Mishra,[||] and S. K. Puri[⊥]

Division of Medicinal and Process Chemistry, Division of Parasitology, and Division of Botany, Central Drug Research Institute, Lucknow-226 001 (U.P), India

tnarender@rediffmail.com

Received September 11, 2007

ABSTRACT



An efficient method is developed for the synthesis of the modified triprenylated chalcone, munchiwarin (1), isolated from the roots of *Crotalaria medicagenia.* The synthesis of 1 utilizes a Claisen–Schmidt condensation between 2,4-dihydroxy-3,5-*C*-diprenyl acetophenone and 4-methoxy benzaldehyde in the presence of $Ba(OH)_2$ to yield the unusual chalcone 5 that contains a nine-membered ether ring. Further prenylation of 5 with 1-bromo-3-methylbut-2-ene and its subsequent demethylation with BBr_3 gave munchiwarin (1).

Chalcones are main precursors for the biosynthesis of a large number of ubiquitous flavonoids, which are frequent components of the human diet. In vitro and in vivo antimalarial[1] and antileishmanial activity[2] has been reported for licochalcone A (Figure 1) isolated from *Glycyrrhiza inflata* Batalin (licorice). Medicagenin **2** isolated from the roots of *Crotalaria medicagenia* DC, exhibits antimalarial activity[3] (Figure 1). 3-Methoxy-4-hydroxy lonchocarpin isolated from the *Lonchocarpus utilis* A.C. Sm. inhibits NADH:ubiquinone oxidoreductase activity (Figure 1).[4]

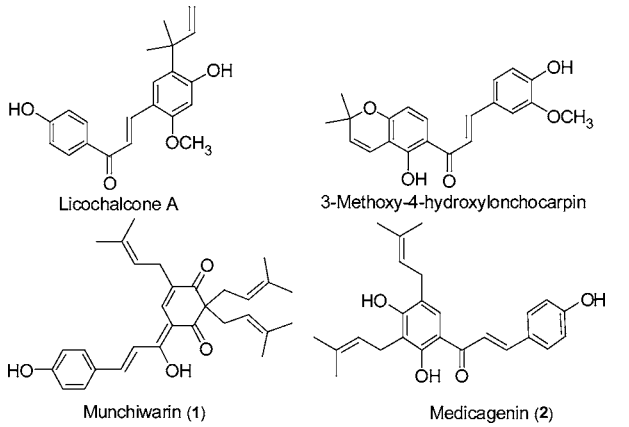


Figure 1. Naturally occurring chalcones: licochalcone A from *Glycyrrhiza inflata* (licorice), 3-methoxy-4-hydroxy lonchocarpin from *Lonchocarpus utilis*, and munchiwarin (**1**) and medicagenin (**2**) from *Crotalaria medicagenia*.

Recent biological evaluation of various chalcones has also revealed anticancer,[5] anti-inflammatory,[6] antimitotic,[7] anti-

* Address correspondence to this author. Phone: +91 522 2612411. Fax: +91 522 2623405.

[#] CDRI Comunication No.7328.

[§] Division of Medicinal and Process Chemistry.

[⊥] Division of Parasitology.

[||] Division of Botany.

[†] Total synthesis of the munchiwarin (**1**) and its analogues.

[‡] Isolation of the munchiwarin (**1**) from *C. medicagenia*.

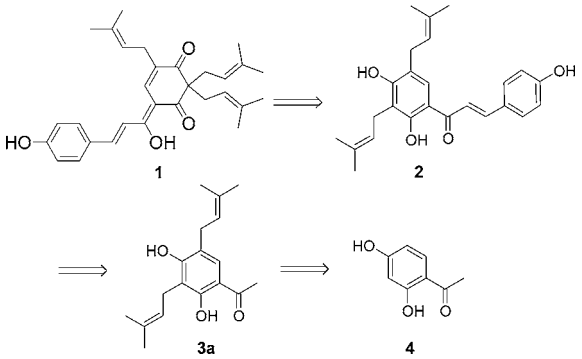
(1) Chen, M.; Theander, T. G.; Christensen, S. B.; Hviid, L.; Zhai, L.; Kharazmi, A. *Antimicrob. Agents Chemother*. **1994**, *38*, 1470.

(2) Chen, M.; Christensen, S. B.; Blom, J.; Lemmich, E.; Nadelmann, L.; Fich, K.; Theander, T. G.; Kharazmi, A. *Antimicrob. Agents Chemother*. **1993**, *37*, 2550. Chen, M.; Christensen, S. B.; Theander, T. G.; Kharazmi. A. *Antimicrob. Agents Chemother*. **1994**, *38*, 1339.

(3) Narender, T.; Shweta; Tanvir, K.; Rao, M. S.; Srivastava, K.; Puri, S. K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2453.

10.1021/ol702187m CCC: $37.00
Published on Web 11/22/2007

Scheme 1



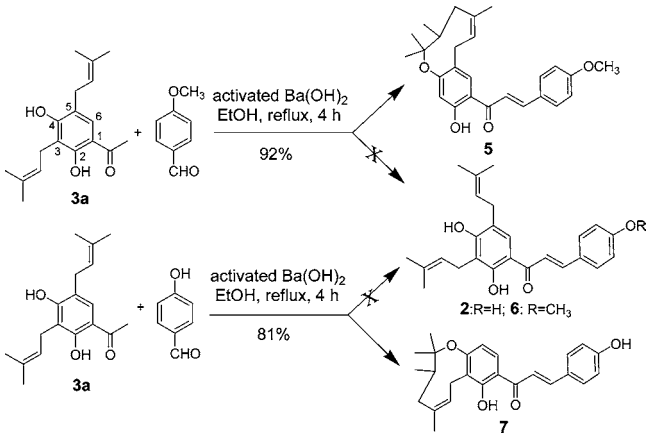
tuberculosis,[8] cardiovascular,[9] cell differentiation inducing,[10] nitric oxide regulation modulatory,[11] and antihyperglycemic activities.[12]

As a part of our ongoing interest in developing new antiparasitic agents, we have recently reported the antimalarial activity of a few naturally occurring prenylated chalcones[3] and the antileishmanial activity of chromenodihydrochalcones.[13]

In continuation of our search for an efficient antimalarial agent, munchiwarin (**1**) was isolated from the roots of *Crotalaria medicagenia* DC (yield: 0.0025% from 1 kg of roots).[14] Munchiwarin (**1**) was the first naturally occurring chalcone with a 2,2,6-triisoprenylcyclohex-5-ene-1,3-dione skeleton previously isolated from another *Crotalaria* species (*C. trifoliastrum*) and characterized by 2D NMR spectroscopy and X-ray crystallography; however, the antimalarial activity was not studied.[15] The goal of the present investigation was to devise and execute a practical synthesis of munchiwarin (**1**) and its analogues and to study their antimalarial activity.

With use of the retrosynthetic strategy outlined in Scheme 1, 2,4-dihydroxy-3,5-*C*-diprenyl acetophenone **3a** was prepared from 2,4-dihydroxy acetophenone **4** and 2-methyl-but-3-en-2-ol with BF_3-Et_2O.[16] It was originally planned to carry out a Claisen−Schmidt condensation between 2,4-dihydroxy-3,5-*C*-diprenyl acetophenone **3a** and 4-methoxy benzaldehyde to obtain the diprenylated chalcone **6** (Scheme 2).

Scheme 2



Further prenylation on the diprenylated chalcone **6** might then provide the triprenylated chalcone **11** and subsequent demethylation of **11** would give desired munchiwarin (**1**). However, the Claisen−Schmidt condensation[17] instead provided the unusual chalcone **5** in 92% isolated yield (Scheme 2), which possesses a nine-membered ether ring. The structure of **5** was confirmed by 2D NMR experiments including HMBC, HSQC, and COSY (Figure 2). Compound

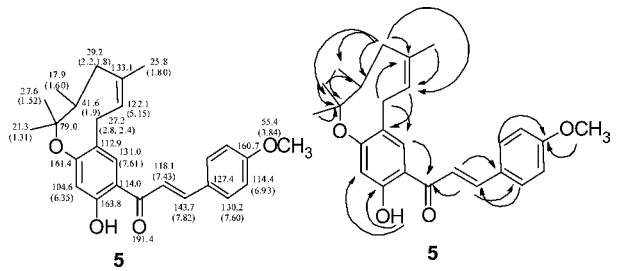


Figure 2. ^1H (in parentheses) and ^{13}C NMR chemical shifts and selected HMBC ($^1H \rightarrow ^{13}C$) correlations of **5**.

5 might be forming by migration of chalcone **6**'s C-3′ prenyl group to the C-4′ hydroxy group via a retro-Claisen rearrangement followed by cyclization of the migrated C-3′ prenyl group and C-5′ prenyl group to give the nine-membered ether ring (Figure 3).

(4) Fang, N.; Casida, J. E. *J. Nat. Prod.* **1999**, *62*, 205.
(5) Xia, Y.; Yang, Z.-Y.; Xia, P.; Bastow, K. F.; Nakanishi, Y.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 699. Bois, F.; Beney, C.; Boumendjel, A.; Mariotte, A.-M.; Conseil, G.; Di Pietro, A. *J. Med. Chem.* **1998**, *41*, 4161.
(6) Hsieh, H.-K.; Tsao, L.-T.; Wang, J.-P. *J.Pharmacol.* **2000**, *52*, 163. Hsieh, H.-K.; Lee, T.-H.; Wang, J.-P.; Wang, J.-J.; Lin, Ch.-N. *Pharma. Res.* **1998**, *15*, 39. Herencia, F.; Ferrándiz, M. L.; Ubeda, A.; Domínguez, J. N.; Charris, J. E.; Lobo, G. M.; Alcaraz, M. J. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1169.
(7) Ducki, S.; Forrest, R.; Hadfield, J. A.; Kendall, A.; Lawrence, N. J.; McGown, A. T.; Rennison, D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1051.
(8) Lin, y.-M.; Zhou, Y.; Flavin, M. T.; Zhou, L.-M.; Nie, W.; Chen, F.-C. *Bioorg. Med. Chem.* **2002**, *10*, 2795.
(9) Furman, C.; Lebeau, J.; Fruchart, J.-C.; Bernier, J.-L.; Duriez, P.; Cotelle, N.; Teissier, E. *J. Biochem. Mol. Toxicol.* **2001**, *15*, 270.
(10) Park, E. J.; Park, H. R.; Lee, J. S.; Kim, J. W. *Planta Med.* **1998**, *64*, 464.
(11) Rojas, J.; Paya, M.; Domínguez, J. N.; Luisa Ferrandiz, M. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1951. Herencia, F.; Ferrandiz, M. L.; Ubeda, A.; Guillen, I.; Domínguez, J. N.; Charris, J. E.; Lobo, G. M.; Alcaraz, M. J. *Free Radical Biol. Med.* **2001**, *30*, 43.
(12) Satyanarayana, M.; Tiwari, P.; Tripathi, B. K.; Srivastava, A. K.; Pratap, R. *Bioorg. Med. Chem.* **2004**, *12*, 883.
(13) Kumar, J. K.; Narender, T.; Rao, M. S.; Rao, P. S.; Toth, G.; Balazs, B.; Duddeck, H. *J. Braz. Chem. Soc.* **1999**, *10*, 278. Narender, T.; Shweta; Gupta, S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3913. Narender, T.; Tanvir, K.; Shweta; Nishi; Goyal, N.; Gupta, S. *Bioorg. Med. Chem.* **2005**, *13*, 6543.
(14) Please see the Supporting Information for the isolation procedure.
(15) Yang, S. W.; Cordell, G. A.; Lotter, H.; Wagner, H.; Mouly, B. C.; Appa Rao, A. V. N.; Rao, P. S. *J. Nat. Prod.* **1998**, *61*, 1274.
(16) Jain, A. C.; Lal, P.; Seshadri, T. R. *Tetrahedron* **1970**, *26*, 2631
(17) Barrios, J.; Marinas, J. M.; Sinisterra, J. V. *Bull. Soc. Chim. Belg.* **1986**, *95*, 107.

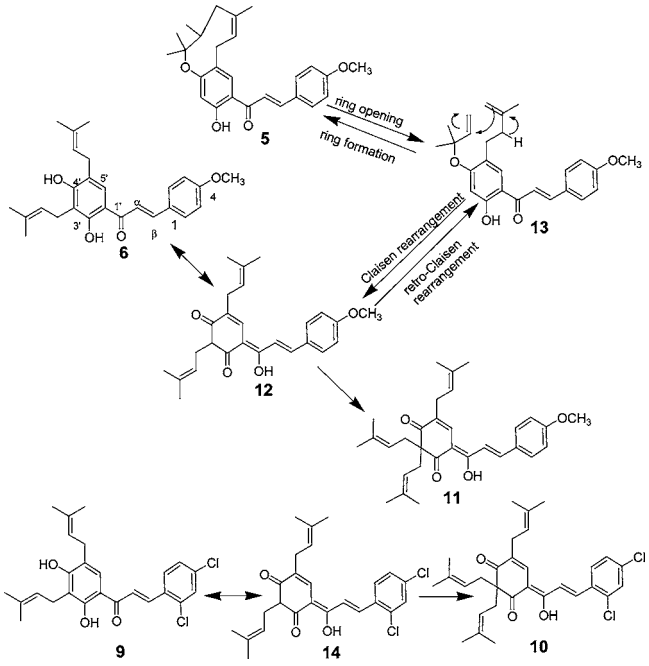


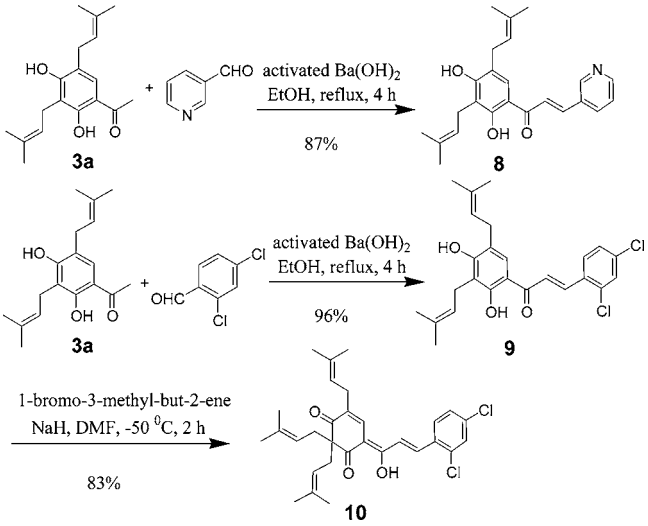
Figure 3. Possible reaction pathway in the formation of chalcones **5**, **10**, and **11**.

Condensation of 2,4-dihydroxy-3,5-*C*-diprenyl acetophenone **3a** with 4-hydroxy benzaldehyde instead of 4-methoxy benzaldehyde led to formation of chalcone **7**, in which migration of the C-5′ prenyl group to the C-4′ hydroxy group (retro-Claisen rearrangement) and subsequent cyclization of the migrated C-5′ prenyl group and C-3′ prenyl group led to a nine-membered ether ring (Scheme 2). To confirm the sequence of reactions (Claisen−Schmidt condensation, retro-Claisen rearragement, and subsequent cyclization) in the formation of **5** and **7**, a reaction was carried out in the absence of benzaldehyde. There was no retro-Claisen rearrangement and subsequent cyclization supports that the Claisen−Schmidt condensation is the first step to give the diprenylated chalcone **2/6** (Figure 3). The extended conjugation in the diprenylated chalcone **2/6** permits further rearrangements to give chalcones **5** and **7** (Scheme 2).

To determine the role of the substituent effect in ring-A a reaction was carried out with aldehydes with deactivating groups instead of ring-A activating groups. Condensation of 2,4-dihydroxy-3,5-*C*-diprenyl acetophenone **3a** with 3-pyridinecarboxaldehyde and 2,4-dichlorobenzaldehyde surprisingly gave chalcones **8** and **9**, respectively (Scheme 3). In the presence of activating groups on ring-A (OMe and OH), prenyl group migration occurs to give **5** and **7**, whereas in the presence of deactivating groups on ring-A reaction occurs without migration to give **8** and **9**.

Further prenylation of **5** by using 1-bromo-3-methylbut-2-ene (prenyl bromide) and NaH in DMF at −50 °C provided *O*-methylmunchiwarin **11** in 95% isolated yield, which possesses three prenyl groups in ring-B (Scheme 4). This might be occurring via opening of the nine-membered ether

Scheme 3

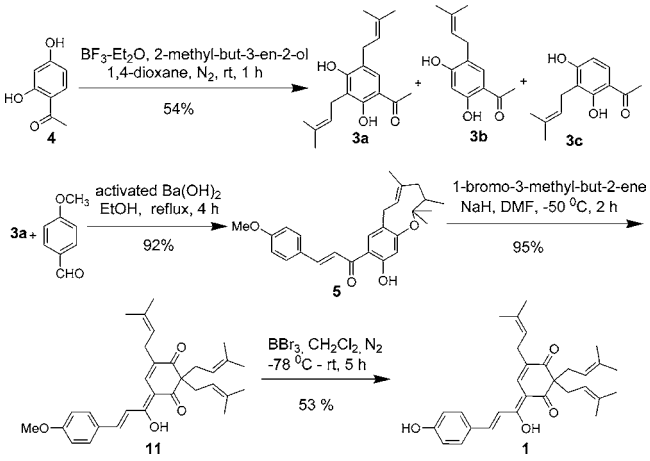


ring and subsequent Claisen rearrangement of the *O*-modified prenyl group (Figure 3) to generate the diketo system in ring B with the activated C-3′ as in **12**. Further prenylation with prenylbromide gave the triprenylated chalcone *O*-methylmunchiwarin **11**. Finally *O*-methylmunchiwarin **11** was demethylated with borontribromide (BBr_3) in anhydrous CH_2Cl_2 at −78 °C to rt to provide the desired munchiwarin (**1**) in 53% isolated yield.

Prenylation of chalcone **9** under similar conditions also provided the triprenylated chalcone **10** with the munchiwarin skeleton (Scheme 3). These results support our proposal that the *O*-methylmuchiwarin **11** and its analogue **10** might have formed through intermediates **12** and **14** (Figure 3), respectively. However, further studies are required to confirm the reaction mechanism.

Munchiwarin (**1**) was evaluated for antimalarial activity[18] against the chloroquine (CQ) sensitive 3D7 strain of *P. falciparum* by SYBR Green based assay[19] and ID_{50} for antimalarial response was determined as 2 μM while the ID_{50}

Scheme 4



for the reference drug, chloroquine, was 0.015 μM in the same assay. The ID_{50} of **1** for cytotoxicity assay[20] against the Vero cell line (C-1008: monkey kidney fibroblast)[21] was determined as 15.1 μM, thus **1** showed a poor therapeutic index (TI) of 7.55.

In summary, we isolated the triprenylated chalcone munchiwarin **1** from the roots of *C. medicagenia* and evaluated its antimalarial activity. We also achieved the first total synthesis of munchiwarin **1** and its analogues **10** and **11** from commercially available 2,4-dihydroxy acetophenone **4**, discovering an unexpected route to the nine-membered ether ring containing chalcones **5** and **7** in the process. Further studies are underway to examine the reaction mechanism, to adjust the conditions to synthesize larger cyclic ether compounds, and to synthesize munchiwarin (**1**) analogues for further biological activity studies.

(18) Evalution of ID_{50} of munchiwarin (**1**): SYBR Green I-based fluorescence (MSF) assay was used. A 200 μL sample of Asynchronous *P. falciparum* parasites at 0.5% parasitemia, 1.5% hematocrit, and varying concentration of munchiwarin (**1**) was incubated at 37 °C for 72 h. After the incubation, 100 μL of lysis buffer [20 mM Tris (pH 7.5), 5 mM EDTA, 0.008% (w/v) saponin, and 0.08% (v/v) Triton X-100] containing SYBR Green I (1 × final concentration) was added to each well and plates were reincubated for another hour at room temperature. The plates were examined for the relative fluorescence units (RFUs) per well using the FLUOstar, BMG labtechnologies. The 50% inhibitory dose (ID_{50}) was determined with GraphPad Prism software by nonlinear regression analysis of log dose−response curves. For both assays, micro titer plate wells containing non-infected erythrocytes in the absence of drugs served as negative control, while parasitized erythrocytes in the presence of chloroquine (CQ) served as positive control.

Acknowledgment. The authors are grateful to the Director of the CDRI in Lucknow, India, for his constant encouragement and support to our program on the isolation of bioactive compounds from the Indian medicinal plants and synthesis of antiparasitic agents. We also thank Dr. Katherine Maloney, UCSD, USA, for editing the manuscript, the SAIF Division for spectral data, J. P. Chaturvedi for technical support, and the CSIR in New Delhi for financial support.

Note Added after ASAP Publication. There was an error in Scheme 4 in the version published ASAP on November 22, 2007; the corrected version was published November 26, 2007.

Supporting Information Available: One- and two-dimensional NMR, mass, and IR spectral data of compounds **1**, **5**, and **11**, and one-dimentional NMR, mass, and IR spectral data of **3a** and **7**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702187M

(19) Smilkstein, M.; Srivilaijaoren, N.; Kelly, J. X.; Wilairat, P.; Risocoe, M. *Antimicrob. Agents Chemother*. **2004**, *48*, 1803.

(20) The cytotoxic activity of munchiwarin (**1**) was determined against the Vero cell line (C-1008; monkey kidney fibroblast) by MTT assay. The cells (1 × 10^4/well) were incubated with varying concentrations of munchiwarin (**1**) for 72 h and inhibitory dose (ID_{50}) values represent the concentration of compound required to kill 50% of the fibroblast cells.

(21) Mosmann, T. *J. Immunol. Methods* **1983**, *65*, 55.