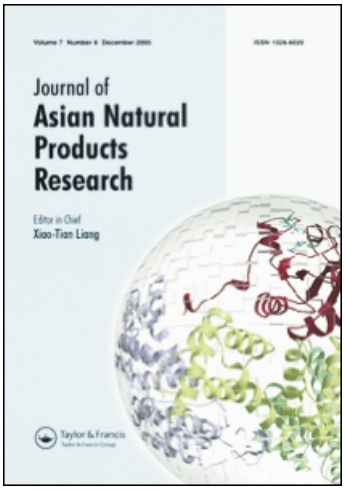


Journal of Asian Natural Products Research
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713454007

Synthesis of (±) homoisoflavanone and corresponding homoisoflavane

Liang Zhang[a]; Wei-Ge Zhang[a]; Jian Kang[a]; Kai Bao[a]; Yi Dai[b]; Xin-Sheng Yao[b]
[a] Department of Medicinal Chemistry, School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang, China [b] The Research Institute of Traditional Chinese Medicines and Natural Products, Jinan University, Guangzhou, China

To cite this Article Zhang, Liang , Zhang, Wei-Ge , Kang, Jian , Bao, Kai , Dai, Yi and Yao, Xin-Sheng(2008) 'Synthesis of (±) homoisoflavanone and corresponding homoisoflavane', Journal of Asian Natural Products Research, 10: 10, 909 — 913
To link to this Article: DOI: 10.1080/10286020802217499
URL: http://dx.doi.org/10.1080/10286020802217499

Journal of Asian Natural Products Research
Vol. 10, No. 10, October 2008, 909–913

Taylor & Francis
Taylor & Francis Group

Synthesis of (±) homoisoflavanone and corresponding homoisoflavane

Liang Zhang[a], Wei-Ge Zhang[a]*, Jian Kang[a], Kai Bao[a], Yi Dai[b] and Xin-Sheng Yao[b]*

[a]*Department of Medicinal Chemistry, School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang 110016, China;* [b]*The Research Institute of Traditional Chinese Medicines and Natural Products, Jinan University, Guangzhou 510632, China*

(*Received 4 January 2007; final version received 24 April 2008*)

The total synthesis of racemic 3-(4′-methoxybenzyl)-7,8-methylenedioxy-chroman-4-one, a homoisoflavanone with antimycobacterial activity isolated recently from *Chlorophytum inornatum*, was described. During this research, the first approach for the conversion of homoisoflavonoids into homoisoflavanes was also developed.

Keywords: homoisoflavanone; antimycobacteria; synthesis; homoisoflavane

1. Introduction

Natural homoisoflavanone compounds, which possess the 3-benzyl-substituted chroman ring system as a common framework, have been isolated from a wide variety of natural sources and exhibit a broad range of biological activities, such as anti-angiogenic activity [1], COX-1 and COX-2 inhibitory activity [2], etc. A new natural homoisoflavanone (Figure 1) (*S*)-3-(4′-methoxybenzyl)-7,8-methylenedioxy-chroman-4-one (**1**) was isolated from *Chlorophytum inornatum*, which exhibited minimum inhibitory values ranging from 16 to 256 μg/ml against four strains of fast-growing mycobacteria [3]. It is well known that the genus *Mycobacterium* is responsible for tuberculosis (TB) and TB is still a very common infectious disease worldwide, particularly in developing countries [4]. In consideration of the reported antimycobacterial activity as well as the lack in the literature of any described total synthesis of either the racemic or optical homoisoflavanone (**1**), we developed a practical route to synthesize the racemic homoisoflavanone ((±) **1**). During this research, we also found a new and straightforward approach to homoisoflavane via the Pd/C-catalyzed hydrogenation/hydrogenolysis of the corresponding homoisoflavone.

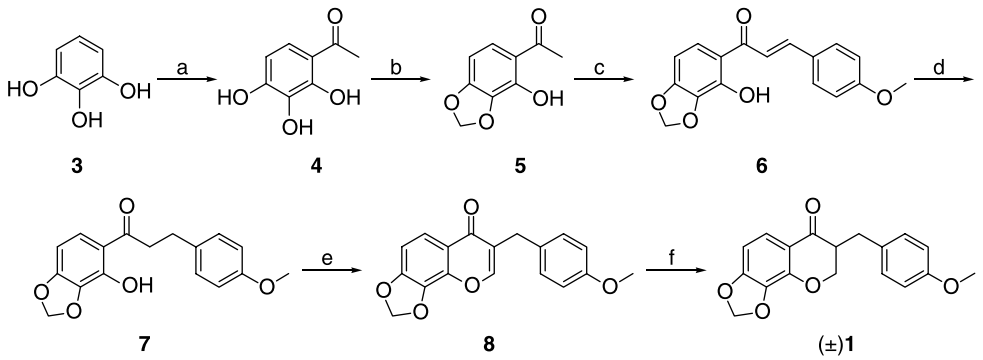
2. Results and discussion

Several methods for the synthesis of homoisoflavanones have been reported in the literatures, which were mainly based on (i) the Friedel–Crafts acylation of racemic or optical 2-benzyl-3-phenoxypropanoic acids in the presence of trifluoroacetic acid and trifluoroacetic anhydride [5], (ii) the catalytic hydrogenation of 3-benzylidenechroman-4-ones obtained via the aldol condensation of 4-chromanones with benzaldehydes [6], (iii) the Michael-type addition of 2-benzyl-1-(2-hydroxyphenyl)prop-2-en-1-one derivatives [7], and (iv) the catalytic hydrogenation of homoisoflavones that could be prepared from dihydrochalcones [8]. In the present work, we employed method (iv) as our strategy for the synthesis of the racemic homoisoflavanone ((±) **1**), which is described in Scheme 1.

*Corresponding authors. Email: zhangweige2000@sina.com; yaoxinsheng@tom.com

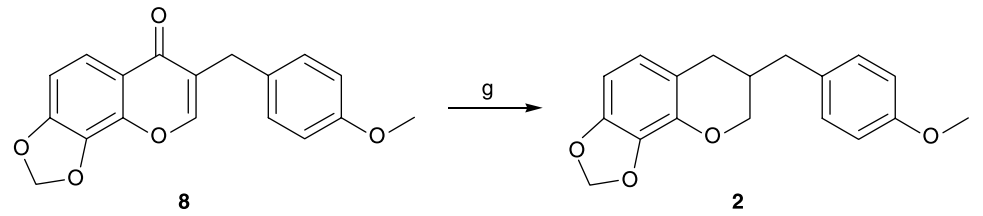
ISSN 1028-6020 print/ISSN 1477-2213 online

DOI: 10.1080/10286020802217499
http://www.informaworld.com



Scheme 1. Reagents and conditions: (a) Ac_2O, H_2SO_4, reflux, 1 h; (b) CH_2Cl_2, K_2CO_3, DMF, reflux, 10 h; (c) 4-methoxybenzaldehyde, 10% NaOH aq, EtOH, rt, 8 h; (d) H_2, Pd/C, THF, rt, 10 h; (e) DMF, $BF_3{\cdot}Et_2O$, PCl_5, 4 h; and (f) H_2, Raney Ni, EtOH, rt, 10 h.

Our synthetic work commenced with the commercially available benzene-1,2,3-triol (**3**) that was acetylated by Ac_2O in the presence of traces of concentrated H_2SO_4 affording ketone (**4**) in 79.7% yield [9]. The synthesis of intermediate (**5**) had been reported in the literature by treating **4** with CH_2I_2 and K_2CO_3 in acetone with a yield less than 10% [10]. When we carried out this reaction using CH_2Cl_2 as an alkylating agent in DMF under reflux, we obtained **5** in 17.1% yield. The aldol condensation of **5** with 4-methoxybenzaldehyde under alkaline condition in EtOH afforded chalcone (**6**) in 61.8% yield, and following hydrogenation using Pd/C as the catalyst in THF at room temperature gave dihydrochalcone (**7**) in 84.5% yield. It had been reported that the conversion of dihydrochalcones into the corresponding homoisoflavones could be achieved by treating them with $(MeO)_2CHNMe_2$ [8], HCOOEt/Na [11], DMF/$MeSO_2Cl$ [12], or DMF/PCl_5 [13]. All methods described above had been tested for the preparation of homoisoflavone (**8**), and the last one was proved to be the most efficient. Thus, the treatment of **7** with DMF and PCl_5 in the presence of Lewis acid, $BF_3{\cdot}Et_2O$, afforded **8** in 71.0% yield. The next step for the synthesis of homoisoflavanone ((±) **1**) was the catalytic hydrogenation of homoisoflavone (**8**). In the pursuit for a suitable catalyst, we came across the use of Raney Ni and Pd/C, two commonly used catalysts in hydrogenation. Raney Ni-catalyzed hydrogenation of **8** in EtOH at atmosphere pressure and room temperature for 12 h gave the racemic homoisoflavanone ((±) **1**) in 80.1% yield, which was identical in ^{1}H NMR and MS with the natural product **1**. However, when we carried out this reaction employing Pd/C as the catalyst in either MeOH or EtOAc, we obtained an unexpected compound as the main product, which was confirmed to be homoisoflavane (**2**) by the ESI-MS and ^{1}H NMR spectra (Scheme 2). This result demonstrated that homoisoflavone (**8**) could be

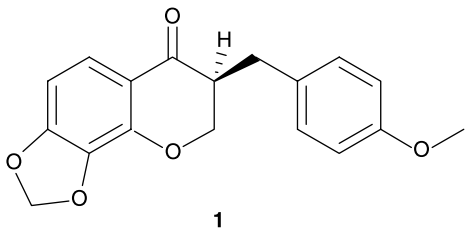


Scheme 2. Reagents and conditions: (g) H_2, Pd/C, MeOH, 12 h.

converted into homoisoflavane (**2**) directly via Pd/C-catalyzed hydrogenation/hydrogenolysis. The influence of solvent, reaction time, and amount of catalyst Pd^0 on the yield of homoisoflavane (**2**) was then examined briefly to optimize the synthetic procedure. The best result with 88.8% yield was obtained when the substrate **8** was reacted in MeOH under H_2 at atmosphere pressure and room temperature in the presence of Pd/C (0.67 equiv.) for 12 h.

Homoisoflavane is a set of rare natural products isolated from several plants of the Agavaceae family, including *Dracaena cinnabari* [14], *D. draco* [15], *D. cochinchinensis* [16], *D. loureiri* [17], and *Agave americana* [18], some of which exhibit interesting and useful biological activities, such as proteasome inhibitory activity [19] and antioxidant activity [20]. However, to date, only a few synthetic methods for the preparation of homoisoflavanes have been documented [21]. Moreover, to the best of our knowledge, the straightforward approach to homoisoflavanes from homoisoflavonoids, a family of compounds that could be synthesized conveniently, had never been reported.

In summary, the first total synthesis of racemic natural homoisoflavanone ((±) **1**) had thus been achieved with a sequence of six steps in 4.0% overall yield. In addition, a new and convenient synthetic approach to homoisoflavanes via the Pd/C-catalyzed hydrogenation/hydrogenolysis of homoisoflavones had been developed. The application of these methodologies toward the homoisoflavanones and homoisoflavones related to the natural product **1** for their structure–activity relationships is currently in progress.



1

Figure 1. Chemical structure of natural homoisoflavanone (**1**).

3. Experimental

3.1 General experimental procedures

Melting points were determined using a hot-stage microscope and are uncorrected. The ^{1}H- and ^{13}C-NMR spectra were taken in $CDCl_3$ solution on Bruker ARX-300 spectrometers with TMS as the internal reference (Bruker BioSciences, Massachusetts, USA). The MS spectra were obtained using Quattro Micro™ spectrometers. Column chromatography was run on silica gel (200–300 mesh) from Qingdao Ocean Chemicals (Qingdao, China). Elemental analyses (C and H) were performed by the Jilin University (Changchun, China). Unless otherwise noted, all the materials were obtained from commercially available sources and were used without further purification.

3.2 1-(2,3,4-Trihydroxyphenyl)ethanone (4)

According to the literature [9], 1-(2,3,4-trihydroxyphenyl)ethanone (**4**) was synthesized with a yield 79.7%, m.p. 171–173°C (169–172°C [9]).

3.3 1-(4-Hydroxybenzo[d][1,3]dioxol-5-yl)ethanone (5)

1-(2,3,4-Trihydroxyphenyl)ethanone (**4**) was treated as the starting material according to the literature [10] using *N*,*N*-dimethylformamide and dichloromethane instead of acetone and methylene iodide. Compound **5** was obtained in 17.1% yield as a white powder; m.p. 84–86°C (85–86°C [10]); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.58 (s, 3H, —CH_3), 6.08 (s, 2H, —OCH_2O—), 6.48 (d, 1H, $J = 8.4$ Hz, Ar-H), 7.39 (d, 1H, $J = 8.4$ Hz, Ar-H), 12.30 (s, 1H, —OH).

3.4 2′-Hydroxy-3′,4′-methylenedioxy-4-methoxychalcone (6)

2′-Hydroxy-3′,4′-methylenedioxy-4-methoxychalcone (**6**) was prepared via a method similar to the literature [10] with a yield of 61.8%; m.p. 142–144°C (143–145°C [10]); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.85 (s, 3H,

—OCH_3), 6.02 (s, 2H, —OCH_2O—), 6.48 (d, 1H, $J = 8.7$ Hz, Ar-H), 6.90 (d, 2H, $J = 9.0$ Hz, Ar-H), 7.38 (d, 1H, $J = 16.8$ Hz, α-H), 7.55 (d, 2H, $J = 9.0$ Hz, Ar-H), 7.80 (d, 1H, $J = 16.8$ Hz, β-H), 8.02 (d, 1H, $J = 8.7$ Hz, Ar-H), 14.04 (s, 1H, —OH). MS (ESI) *m/z*: 299 $[M + H]^+$.

3.5 2′-Hydroxy-3′,4′-methylenedioxy-4-methoxydihydrochalcone (7)

Compound **6** (1.27 g, 4.26 mmol) was dissolved in THF (40 ml) and to this was added 10% Pd/C (0.13 g). The mixture was stirred at room temperature under H_2 atmosphere for 10 h. After filtration, the liquid was concentrated *in vacuo* and the residue obtained was purified by column chromatography over silica gel to give **7** (1.08 g, 84.5%) as a white powder; m.p. 82–84°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.03 (t, 2H, β-CH_2, $J = 7.5$ Hz), 3.21 (t, 2H, α-CH_2, $J = 7.5$ Hz), 3.86 (s, 3H, —OCH_3), 6.04 (s, 2H, —OCH_2O—), 6.48 (d, 1H, $J = 8.7$ Hz, Ar-H), 6.90 (d, 2H, $J = 9.0$ Hz, Ar-H), 7.55 (d, 2H, $J = 9.0$ Hz, Ar-H), 8.02 (d, 1H, $J = 8.7$ Hz, Ar-H), 14.01 (s, 1H, —OH). MS (ESI) *m/z*: 323 $[M + Na]^+$. Elemental analysis: Found: C, 67.91%; H, 5.40%; Calcd for $C_{17}H_{16}O_5$: C, 67.99%; H, 5.37%.

3.6 3-(4′-Methoxybenzyl)-7,8-methylenedioxy-4H-chromen-4-one (8)

A mixture of **7** (0.91 g, 3.01 mmol) and $BF_3{\cdot}Et_2O$ (1.2 ml, 9.02 mmol) was cooled to 8–10°C and DMF (4.6 ml) was added dropwise for 5 min. In another flask, DMF (8 ml) was cooled to 10°C and PCl_5 (0.939 g, 4.50 mmol) was added in small portions. The mixture was then allowed to stand at room temperature for 20 min. The light yellow-colored solution was then added to the above reaction mixture slowly at 20–23°C. The mixture was stirred at room temperature for 4 h and poured into boiling dilute HCl slowly and cooled. The solution was extracted with EtOAc (3 × 50 ml) and the combined organic layer was washed with water (20 ml), brine (20 ml), and dried over sodium sulfate. The residue obtained after the evaporation of the solvent was chromatographed over silica gel column to give **8** (0.66 g, 71.0%) as a white solid; m.p. 164–166°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.73 (s, 2H, —CH_2—Ar), 3.79 (s, 3H, —OCH_3), 6.16 (s, 2H, —OCH_2O—), 6.85 (d, 2H, $J = 8.7$ Hz, Ar-H), 6.93 (d, 1H, $J = 8.4$ Hz, Ar-H), 7.21 (d, 2H, $J = 8.7$ Hz, Ar-H), 7.51 (s, 1H, —OCH═), 7.81 (d, 1H, $J = 8.4$ Hz, Ar-H). ^{13}C NMR ($CDCl_3$) δ: 30.8, 55.3, 103.2, 107.1, 114.0, 114.0, 120.0, 120.5, 124.5, 130.0, 130.0, 130.4, 134.4, 141.5, 152.1, 152.1, 158.3, 176.5. MS (ESI) *m/z*: 311 $[M + H]^+$. Elemental analysis: Found: C, 69.74%; H, 4.51%; Calcd for $C_{18}H_{14}O_5$: C, 69.67%; H, 4.55%.

3.7 3-(4′-Methoxybenzyl)-7,8-methylenedioxy-chroman-4-one (1)

To a solution of **8** (0.20 g, 0.68 mmol) in EtOH (10 ml) was added the suspension of Raney Ni (0.04 g) in EtOH (0.5 ml). The mixture was stirred at room temperature for 10 h, and then it was filtered. The removal of the solvent yielded a residue that was purified by column chromatography over silica gel to give **1** (0.17 g, 80.1%) as a white powder; m.p. 105–107°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.74 (dd, 1H, $J = 13.5$, 10.5 Hz, —CH_2—Ar,), 2.86 (m, 1H, —CH—), 3.21 (dd, 1H, $J = 13.5$, 4.2 Hz, —CH_2—Ar), 3.83 (s, 3H, —OCH_3), 4.27 (dd, 1H, $J = 11.4$, 7.2 Hz, —OCH_2—), 4.44 (dd, 1H, $J = 11.4$, 3.9 Hz, —OCH_2—), 6.12 (s, 2H, —OCH_2O—), 6.64 (d, 1H, $J = 8.4$ Hz, Ar-H), 6.89 (d, 2H, $J = 8.7$ Hz, Ar-H), 7.19 (d, 2H, $J = 8.7$ Hz, Ar-H), 7.62 (d, 1H, $J = 8.4$ Hz, Ar-H). ^{13}C NMR ($CDCl_3$) δ: 31.8, 48.0, 55.4, 69.9, 102.7, 103.3, 114.1, 114.1, 117.5, 123.2, 130.1, 130.1, 130.2, 134.6, 145.5, 153.8, 158.4, 192.0. MS (ESI) *m/z*: 313 $[M + H]^+$. Elemental analysis: Found: C, 69.10%; H, 5.23%; Calcd for $C_{18}H_{16}O_5$: C, 69.22%; H, 5.16%.

3.8 3-(4′-Methoxybenzyl)-7,8-methylene-dioxychroman (2)

A solution of **8** (0.20 g, 0.68 mmol) in EtOH (10 ml) and 10% Pd/C (0.02 g) were stirred at room temperature for 12 h, and then it was filtered. The liquid was concentrated under removed pressure and the residue was purified by column chromatography over silica gel to give **2** (0.18 g, 88.8%) as a white solid; m.p. 94–96°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.28 (m, 1H, —CH—), 2.42–2.78 (m, 4H, —CH_2—Ar), 3.80 (s, 3H, —OCH_3), 3.87 (dd, 1H, $J = 10.2$, 8.7 Hz, —OCH_2—), 4.24 (dd, 1H, $J = 10.2$, 3.0 Hz, —OCH_2—), 5.94 (d, 2H, $J = 3.0$ Hz, —OCH_2O—), 6.40 (d, 1H, $J = 8.1$ Hz, Ar-H), 6.48 (d, 1H, $J = 8.1$ Hz, Ar-H), 6.85 (d, 2H, $J = 8.4$ Hz, Ar-H), 7.10 (d, 2H, $J = 8.4$ Hz, Ar-H). ^{13}C NMR ($CDCl_3$) δ: 30.5, 34.3, 37.0, 55.3, 70.3, 101.4, 101.4, 113.9, 113.9, 116.9, 121.9, 129.9, 129.9, 131.2, 134.2, 139.1, 146.9, 158.2. MS (ESI) *m/z*: 321 $[M + Na]^+$. Elemental analysis: Found: C, 72.39%; H, 6.04%; Calcd for $C_{18}H_{18}O_4$: C, 72.47%; H, 6.08%.

References

[1] J.S. Shim, J.H. Kim, J. Lee, S.N. Kim, and H.J. Kwon, *Planta Med.* **70**, 171 (2004).

[2] K. Likhitwitayawuid, K. Sawasdee, and K. Kirtikara, *Planta Med.* **68**, 841 (2002).

[3] G. O'Donnell, F. Bucar, and S. Gibbons, *Phytochemistry* **67**, 178 (2006).

[4] *WHO Global Tuberculosis Control Report*, (World Health Organization, Geneva, March 2002).

[5] M. Kawasaki, N. Toyoka, Y. Matsui, A. Tanaka, M. Goto, H. Kakuda, S. Kawabata, and T. Kometani, *Heterocycles* **65**, 761 (2005).

[6] A. Arnoldi, A. Bassoli, G. Borgonovo, and L. Merlini, *J. Chem. Soc. Perkin Trans. 1* **19**, 2447 (1995).

[7] S. Jaspal and S.K. Grover, *Indian J. Chem. Sect. B: Org. Chem. Incl. Med. Chem.* **43B**, 1782 (2004).

[8] B.S. Kirkiacharian and M. Gomis, *Synth. Commun.* **35**, 563 (2005).

[9] Y.K. Rao, C.V. Rao, P.H. Kishore, and D.J. Gunasekar, *J. Nat. Prod.* **64**, 368 (2001).

[10] V.S. Parmar, S. Singh, and R. Jain, *J. Chem. Sect. B: Org. Chem. Incl. Med. Chem.* **26B**, 166 (1987).

[11] F.A. Davis and B.C. Chen, *J. Org. Chem.* **58**, 1751 (1993).

[12] K.A. Ismail and T.A. El Aziem, *Eur. J. Med. Chem.* **36**, 243 (2001).

[13] V. Siddaiah, C.V. Rao, S. Venkateswarlu, and G.V. Subbaraju, *Tetrahedron* **62**, 841 (2006).

[14] G. Adam, M. Masaoud, H. Ripperger, U. Himmelreich, and J. Schmidt, *Proceedings of the Plant Growth Regulator Society of America*, 22nd (Plant Growth Regulator Society of America, San Francisco, 1995), pp. 142–146.

[15] A.G. Gonzalez, F. Leon, L. Sanchez-Pinto, J.I. Padron, and J. Bermejo, *J. Nat. Prod.* **63**, 1297 (2000).

[16] Q.A. Zheng, H.Z. Li, Y.J. Zhang, and C.R. Yang, *Helv. Chim. Acta* **87**, 1167 (2004).

[17] D. Meksuriyen, G.A. Cordell, N. Ruangrungsi, and P. Tantivatana, *J. Nat. Prod.* **50**, 1118 (1987).

[18] W.F. Tinto, J.L. Simmons-Boyce, S. Mclean, and W.F. Reynolds, *Fitoterapia* **76**, 594 (2005).

[19] S. Tsukamoto, T. Wakana, K. Koimaru, T. Yoshida, M. Sato, and T. Ohta, *Biol. Pharm. Bull.* **28**, 1798 (2005).

[20] M. Machala, R. Kubinova, P. Haoravova, and V. Suchy, *Phytoth. Res.* **15**, 114 (2001).

[21] S. Usse, G. Guillaumet, and M.C. Viaud, *Tetrahedron Lett.* **38**, 5501 (1997).