A New Synthesis of Angelicin from 7-Hydroxycoumarin *via* *C*-Propenation-*O*-Vinylation and Ring-Closing Metathesis

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A new and concise method for the synthesis of angelicin was described. 7-Hydroxycoumarin was converted into angelicin in good overall yields *via* the process of *c*-propenation-*o*-vinylation and ring-closing metathesis (RCM).

Keywords: Claisen rearrangement; RCM; Angelicin.

INTRODUCTION

Angelicin, 2*H*-furo[2,3-*h*]chromene-2-one, a naturally occurring furanocoumarin is present in the seeds,[1] and the leaves[2] of *Psoralea grandulosa*, and in addition displays a wide variety of potent and interesting biological activities. These include antifungal activities,[3] inducing S-phase delay in the *rad 14* Δ mutant,[4] inhibition of mutagenesis of 2-amino-3-methylimidazo[4,5-*f*]quinoloine,[5] inhibitory effects on the biotransformation of aflatoxin B_1 to aflatoxin B_1-8,9-epoxide,[6] and inhibition of inducible nitric oxide synthase.[7] Major synthetic strategies utilized include the following: (i) pyrolysis (650 °C, 0.001 Torr) of methyl 3-(7-allyloxycoumarin-8-yl)propenoate prepared from 7-hydroxycoumarin by 3 steps,[8] (ii) vinylation of 8-halo-7-hydroxycoumarins, followed by oxidization with $Tl(NO_3)_3$ in methanol, and finally by the treatment with acid,[9] (iii) *via* the benzannulation reaction of furylcarbene complexes of chromium,[10,11] (iv) dihydrobenzofuran derivatives as starting material to build the α-pyrone ring through related reactions,[12] and (v) *via* Suzuki or Sonogashira cross-coupling reaction of corresponding triflate.[13] However those methods still have some disadvantages, including the tedious reaction conditions, the low yield, and the intermediate which is commercially unavailable and difficult to prepare. Thus, it is necessary to develop a more efficient method for the title compound. Until present, no attention has been paid to apply the RCM reaction, which has been widely utilized in many aspects in organic synthesis,[14] to the synthesis of angelicin. In this our continuing studies, herein we would like to disclose a new method for the preparation of angelicin by the following protocols (Scheme I): (i) 7-allyloxycoumarin (**2**), prepared from 7-hydroxycoumarin (**1**), was subjected to the Claisen rearrangement to furnish *c*-allylation to give 8-allyl-7-hydroxycoumarin (**3**) as major product; (ii) subsequently compound **3** was allowed to react with excess 1,2-dichloroethane in the presence of potassium carbonate to undergo *o*-chloroethylation to give the monochloroethylated product, 8-allyl-7-(2-chloroethoxy)coumarin (**6**); (iii) by the treatment of compound **6** with potassium *tert*-butoxide to undergo the isomerization of allyl group to give *c*-propenyl function and to eliminate HCl from chloroethyl group to afford *o*-vinyl function in one pot, briefly established an intramolecular dienes, 8-(1-propenyl)-7-vinyloxycoumarin (**7**) as the precursor of RCM; (iv) finally by the cyclization of compound **7** with Grubbs' catalyst to undergo RCM gave compound **8**, angelicin, in good overall yields.

RESULTS AND DISCUSSION

7-Allyloxycourmarin (**2**), prepared from allyllation of 7-hydroxycoumarin (**1**) as the general procedure[15] in yields of 95%, was subjected to the Claisen rearrangement with various conditions to give 8-allyl-7-hydroxycoumarin (**3**) as major product, and 6-allyl-7-hydroxycoumarin (**4**), together with 8-methyl-8,9-dihydrofuro[2,3-*h*]chromen-2-one (**5**) as minor products. Some reaction conditions of the Claisen rear-

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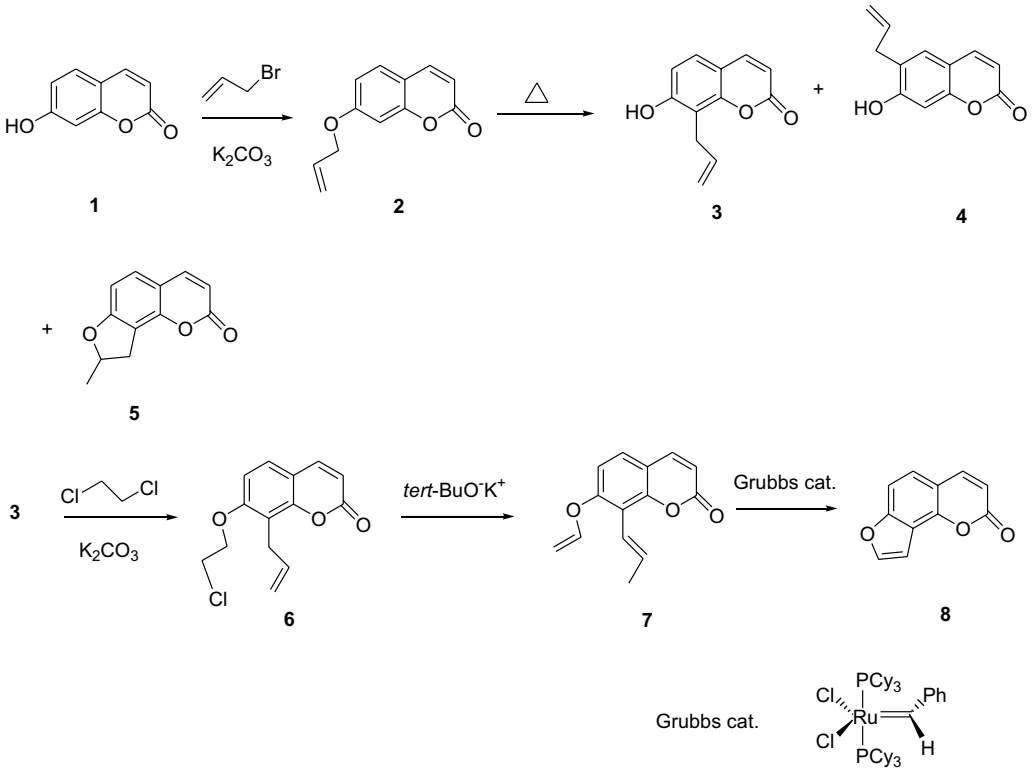
Scheme I



rangement of 7-allyloxycoumarin (**2**) have been reported, such as heating to reflux in *N,N*-diethylaniline in a closed vessel, and in refluxing ethylene glycol. However only 8-allyl-7-hydroxycoumarin (**3**) was obtained and reported in 84% yields or in 94% crude yields in the condition of refluxing in *N,N*-diethylaniline[16] or in a closed vessel,[17] respectively. On the other hand, not only 8-allyl-7-hydroxycoumarin (**3**) in 70% yields but also 6-allyl-7-hydroxycoumarin (**4**) in 20% yields was obtained if in refluxing ethylene glycol.[18] The minor product, 8-methyl-8,9-dihydrofuro-[2,3-*h*]chromen-2-one (**5**) was paid no attention in running the Claisen rearrangement of 7-allyloxycoumarin (**2**) in the previous studies. The reaction conditions of our studies and results of the Claisen rearrangement of compound **2** are compiled in Table 1.

These isomers have identical molecular weights, but have different ^{1}H-NMR spectra, which can be easily identified. For example, both compound **3**, and compound **4** are coincident with the spectral data reported in the previous studies.[16,17] However, compound **5**, which was paid no attention in the related Claisen rearrangement,[16,17] exhibited the same spectral data in both proton-NMR and carbon-13 NMR reported by different approaches.[19] Subsequently 8-allyl-7-hydroxycoumarin (**3**) dissolved in dry acetone was reacted with excess 1,2-dichloroethane under mild reflux in the presence of anhydrous K_2CO_3 for 8 h, to undergo monochloroethylation to give 8-allyl-7-(2-chloroethoxy)coumarin (**6**) as the sole product, in yields of 92%. In the case of running the monochloroethylation of compound **3** with two phases reaction as in our previous report,[20] no desired compound **6** was found due to the opening of the coumarin ring. The structure of compound **6** can be verified as the following spectral data. For example, ^{1}H-NMR ($CDCl_3$, 200 MHz) the selected signals showed three double doublet signals at 3.64 ppm (J = 6.6, 1.4 Hz, 2H), 5.0 ppm (dd, $J_{cis\text{-}gem}$ = 10.0, 1.8 Hz, 1H), and 5.11 ppm (dd, $J_{trans\text{-}gem}$ = 17.0, 1.8 Hz, 1H), together with one multiplet signal at 5.98 ppm (1H), indicating the presence of an allyl group in the molecule. Furthermore two triplet signals, each one has two protons, respectively at 3.87 ppm (t, J = 5.8 Hz, 2H), and 4.33 pm (t, J = 5.8 Hz, 2H) indicating the presence of the OCH_2CH_2Cl function. Furthermore, the spectral data of ^{13}C-NMR ($CDCl_3$, 50 MHz) revealed fourteen carbons, matching the carbon required for compound **6**. Subsequently, the treatment of compound **6** with one and half equivalents of potassium *tert*-butoxide at ambient temperature isomerized the double bond of allyl group and concomitantly eliminated HCl from the chloroethyl group to generate 8-(1-propenyl)-7-vinyloxycoumarin (**7**) as the precursor of

Table 1. The Claisen rearrangement of 7-allyloxycoumarin (**2**) under various conditions gave compounds **3**, **4**, and **5** in yields of various ratios

Methods*	Compound **3** (% yield)**	Compound **4** (% yield)**	Compound **5** (% yield)**
A. Neat	57.1%	4.1%	8.9%
B. *N,N*-diethylaniline***	77.0%	11.8%	9.1%
C. Decalin	51.5%	12.1%	34.0%
D. Diphenyl ether	53.3%	10.7%	21.4%
E. *N,N*-Diethylaniline + silical gel****	68.4%	8.2%	4.3%

* Method A, under argon it was heated at 160 °C without any solvent for 3 h, if heated at higher temperature, a dark black mass was obtained; Method B, under reflux in *N,N*-diethylaniline for 3 h; Method C, under reflux in decalin for 3 h; Method D, under reflux in diphenyl ether for 3 h; Method E, under reflux in *N,N*-diethylaniline and silica gel for 3 h. ** Percentage yields were determined by the isolated yields. *** The yields obtained are lower than that of the same reaction condition previously reported by Clarke, D. J. et al.[16] **** When an amount of silica gel (1.5 × of compound **2** in weight) was added in carrying out the Claisen rearrangement, no improvement of the percentage yields of the desired compound **3** was observed.

RCM in 60% yield in one pot. The evidence of structure **7** was based on the spectral data. For example, ^{1}H-NMR ($CDCl_3$, 200 MHz): the selected signals showed one methyl signal with double doublet at 1.98 ppm (J = 6.6, 1.8 Hz) indicating the migration of allylic double bond from terminal end to internal one, and three one-proton olefinic signals with double doublet, respectively at 4.58 ppm (dd, $J_{cis\text{-}gem}$ = 6.0, 2.0 Hz), 4.86 ppm (dd, $J_{trans\text{-}gem}$ = 13.6, 2.0 Hz), 6.61 ppm (dd, $J_{trans\text{-}cis}$ = 13.6, 6.0 Hz) exhibiting the presence of one vinyl group in the molecule of compound **7**. Furthermore, fourteen carbons in the ^{13}C-NMR spectrum and *m/z* 228 (M^+) in the EI-MS (70 eV) spectrum, that all coincident with the molecular formula, $C_{14}H_{12}O_3$ required for compound **7**, were found. Finally, the ring-closing metathesis with Grubbs' catalyst gave angelicin (**8**) in yields of 90%. All data obtained from compound **8** are matched with that of the natural product, angelicin.[11]

In conclusion, based on the Claisen rearrangement of 7-allyloxycoumarin, *via* a sequence of reactions to easily build up the precursor of RCM, and followed by olefin ring-closing metathesis, successfully gave angelicin in 36% overall yields. The application of our synthetic strategy to the preparation of some potential compounds is currently in progress in our laboratory.

EXPERIMENTAL

Melting points (Yanaco micro melting-point apparatus) are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Varian Gemini-200 or Varian Unity Plus 400 spectrometers using $CDCl_3$ as solvent, and with TMS as the internal standard. MS were recorded on Chem/hp/middle instrument, and HRMS were recorded on JEOL, JMSD-200 or on JEOL, JMS-SX. Elemental analyses were recorded on a Heraeus CHN-O Rapid Analyzer. Silica gel (230-400 mesh) for column chromatography and precoated silica gel plates (60F-254) for TLC were purchased from E. Merck. UV light (254 nm) was used to detect spots on TLC plates after development. Grubbs' catalyst was purchased from Fluca Company, and 7-hydroxycourmarin was purchased from Acros Company.

7-Allyloxycoumarin (**2**),[15,16] 8-allyl-7-hydroxycoumarin (**3**),[16] 6-allyl-7-hydroxycoumarin (**4**),[18] and 8-methyl-8,9-dihydrofuro[2,3-*h*]chrome-2-one (**5**)[19] were known compounds, and prepared as in general procedures, respectively.

Preparation of 8-Allyl-7-(2-chloroethoxy)coumarin (6)

To 8-allyl-7-hydroxycoumarin, compound **4** (10.1 g, 0.05 mol), dissolved in dry acetone (100 mL) was added with anhydrous K_2CO_3 (17.25 g, 0.125 mol) and under reflux for 20 min., then was injected with excess 1,2-dichloroethane (59 mL, 0.75 mol). The mixture was under reflux for 48 h, and then was filtered through Celite 545. The filtrate was concentrated under vacuum. The residue was dissolved in ethyl acetate (100 mL), and washed with brine (20 mL × 3). The organic solution was dried with anhydrous $MgSO_4$, and then was filtered. The filtrate was concentrated, and the residue was subjected to silica gel chromatographic column (EtOAc/*n*-hexane = 1/2) to give pure 8-allyl-7-(2-chloroethoxy)coumarin (**6**).

Pure **8-allyl-7-(2-chloroethoxy)coumarin** (**6**) (12.2 g, 92%) was obtained as colorless needle crystals, mp 142 °C, R_f 0.4 (EtOAc/*n*-hexane = 1/2), ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 3.64 (dd, *J* = 6.6, 1.4 Hz, 2H, C$\underline{H}_2$CH=CH_2), 3.87 (t, *J* = 5.8 Hz, 2H, $OCH_2C\underline{H}_2Cl$), 4.33 (t, *J* = 5.8 Hz, 2H, $OC\underline{H}_2CH_2Cl$), 5.0 (dd, $J_{cis\text{-}gem}$ = 10.0, 1.8 Hz, 2H, $CH_2CH=CH_2$), 5.11 (dd, $J_{trans\text{-}gem}$ = 17.0, 1.8 Hz, 1H, $CH_2CH=C\underline{H}_2$), 5.98 (m, 1H, $CH_2C\underline{H}=CH_2$), 6.27 (d, *J* = 9.5 Hz, H-3), 6.82 (d, *J* = 8.6 Hz, 1H, H-6), 7.33 (d, *J* = 8.6 Hz, 1H, H-5), 7.64 (d, *J* = 9.5 Hz, H-4); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 26.94, 41.69, 68.73, 108.29, 113.46, 113.52, 115.65, 116.86, 126.63, 134.95, 143.54, 153.00, 158.82, 161.05; EI-MS 266 (M^{+2}, 20), 264 (M^+, 64), 229 (67), 201 (37), 187 (100), 173 (62), 159 (57), 128 (32), 115 (45); Anal calcd for $C_{14}H_{13}ClO_3$: C, 63.52; H, 4.95. Found: C, 63.46; H, 5.06.

Preparation of 8-(1-propenyl)-7-(vinyloxy)coumarin (7)

Under dry nitrogen 8-Allyl-7-(2-chloroethoxy)coumarin (10 g, 38 mmol), dissolved in anhydrous THF (80 mL), was added potassium *tert*-butoxide (6.4 g, 57 mmol) and stirred at ambient temperature for 5 h. After the end of reaction, the suspension was filtered, and washed through filter paper with ethyl acetate (25 mL × 3). The organic filtrate was dried with $MgSO_4$. After filtration, the solution was concentrated under vacuum; the resulting residue was subjected to silica gel chromatographic column (EtOAc/*n*-hexane = 1:2) to give pure 8-(1-Propenyl)-7-(vinyloxy)coumarin (**7**).

Pure **8-(1-propenyl)-7-(vinyloxy)coumarin** (**7**) (5.2 g, 60%) was obtained as colorless crystals, mp 102 °C, R_f 0.4 (EtOAc/*n*-hexane = 1/2), ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.98 (dd, *J* = 6.6, 1.8 Hz, 3H, CH=CHC$\underline{H}_3$), 4.58 (dd, $J_{cis\text{-}gem}$ = 6.0, 2.0 Hz, 1H, OCH=C$\underline{H}_2$), 4.86 (dd, $J_{trans\text{-}gem}$ = 13.6, 2.0 Hz, 1H, OCH=C$\underline{H}_2$), 6.30 (d, *J* = 9.6 Hz, H-3), 6.61 (dd, $J_{trans\text{-}cis}$ = 13.6, 6.0 Hz, 1H, OC$\underline{H}$=CH_2), 6.67 (dq, *J* = 16.0, 1.8 Hz, 1H, C$\underline{H}$=$CHCH_3$), 6.84 (dq, *J* = 16.0, 6.6 Hz, 1H, CH=C$\underline{H}CH_3$), 6.91 (d, *J* = 8.6 Hz, 1H, H-6), 7.25 (d, *J* = 8.6 Hz, 1H, H-5), 7.64 (d, *J* = 9.6 Hz, H-4); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 20.15, 97.07, 113.077, 114.15, 114.74, 116.40, 118.57, 126.05, 134.47, 143.68, 147.42, 152.30, 156.54, 160.68; EI-MS (70 eV) *m/z* 228 (M^+, 48), 213 (29), 200 (24), 199 (100), 186 (29), 185 (22), 171 (30), 158 (39), 128 (31), 115 (23); Anal calcd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.64; H, 5.41.

Preparation of Angelicin (8)

To compound **7**, 8-(1-propenyl)-7-(vinyloxy)courmarin (3 g, 13 mmol) dissolved in anhydrous CH_2Cl_2 (150 mL) (0.08 M), was added Grubbs catalyst (0.1 g, 1% mole). The mixture was stirred for 72 h at ambient temperature under dry argon. Finally the solvent was removed *in vacuo*, and the resulting residue was subjected to a silica gel chromatographic column (EtOAc/*n*-hexane = 1/2) or to be distilled under vacuum to give pure angelicin (**8**).

Angelicin (**8**) (2.17 g, 90%) was obtained as colorless needle crystals: bp = 98-104 °C (4 mmHg), mp 139 °C [lit.,[13] 137-137.5], R_f 0.44 (EtOAc/*n*-hexane = 1/2), ^{1}H-NMR ($CDCl_3$, 200 MHz) δ 6.40 (d, *J* = 9.6 Hz, 1H, H-3), 7.14 (dd, *J* = 2.2, 0.6 Hz, 1H, H-9), 7.38 (d, *J* = 8.5 Hz, 1H, H-5), 7.45 (dd, *J* = 8.5, 0.6 Hz, 1H, H-6), 7.70 (d, *J* = 2.2 Hz, H-8), 7.82 (d, *J* = 9.6 Hz, 1H, H-4), ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 104.07, 108.77, 113.51, 114.11, 116.92, 123.80, 114.45, 145.86, 148.51, 157.34, 160.77, EI-MS (70 eV) *m/z* 186 (M^+, 83), 159 (12), 158 (100), 130 (24), 102 (41). Anal calcd for $C_{11}H_6O_3$: C, 70.97; H, 3.25. Found: C, 70.99; H, 3.42.

ACKNOWLEDGEMENTS

We are grateful to NSC, Taiwan, for financial support, to Mr. Wen-Hsiung Lu for measuring elemental analysis, and to Miss Chyi-Jia Wang for recording proton and carbon NMR spectra.

Received January 13, 2004.

REFERENCES

1. Lin, Y. L.; Kuo, Y. H. *Heterocycles* **1992**, *34*, 1555.
2. Labbe, C.; Faini, F.; Coll, J.; Connolly, J. D. *Phytochemistry* **1996**, *42*, 1299.
3. Sardari, S.; Mori, Y.; Horita, K.; Micetich, R. G.; Nishibe, S.; Daneshtalab, M. *Bioorg. Med. Chem.* **1999**, *7*, 1933.
4. Grossmann, K. F.; Ward, A. M.; Matkovic, M. E.; Folias, A. E.; Moses, R. E. *Mutat. Res*. **2001**, *487*, 73.
5. Edenharder, R.; Speth, C.; Decker, M.; Kolodziej, H.; Kayser, O.; Platt, K. L. *Mutat. Res*. **1995**, *345*, 57.
6. Lee, S. E.; Campbell, B. C.; Molyneux, R. J.; Hasegawa, S.; Lee, H. S. *J. Agric. Food Chem.* **2001**, *49*, 5171.
7. Wang, C. C.; Lai, J. E.; Chen, L. G.; Yen, K. Y.; Yang, L. L. *Bioorg. Med. Chem*. **2000**, *8*, 2701.
8. Black, M.; Cadogan, J. I. G.; McNab, H.; Macpherson, A. D.; Roddam, V. P.; Smith, C.; Swenson, H. R. *J. Chem. Soc. Perkin Trans. 1* **1997**, *17*, 2483.
9. Harayama, T.; Nishita, Y. *Chem. Pharm. Bull*. **1996**, *44*, 1986.
10. Peterson, G. A.; Kunng, F. A.; McCallum, S. J.; Wulff, W. D.

Tetrahedron Lett. **1987**, *28*, 1381.
11. Wulff, W. D.; McCallum, J. S.; Kunng, F. A. *J. Am. Chem. Soc.* **1988**, *110*, 7419.
12. Lee, Y. R. *Tetrahedron* **1995**, *51*, 3087.
13. Hesse, S.; Kirsch, G. *Tetrahedron Lett*. **2003**, *44*, 97.
14. (a) Huang, K. S.; Wang, E. C. *Tetrahedron Lett*. **2001**, *42*, 6155. (b) Huang, K. S.; Wang, E. C.; Chen, H. M. *J. Chin. Chem. Soc.* **2004**, 383. (c) Huang, K. S.; Chen, H. M.; Wang, E. C. *J. Chin. Chem. Soc.* **2004**, 585. (d) Huang, K. S.; Wang, E. C. *J. Chin. Chem. Soc.* **2004**, 807. (e) Wang, E. C.; Hsu, M. K.; Lin, Y. L.; Huang, K. S. *Heterocycles* **2002**, *57*, 1997. (f) Wang, E. C.; Wang, C. C.; Hsu, M. K.; Huang, K. S. *Heterocycles* **2002**, *57*, 2021. (g) Wang, E. C.; Huang, K. S.; Lin, G. W.; Lin, J. R.; Hsu, M. K. *J. Chin. Chem.* **2001**, *48*, 83.
15. Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*; 5th. Ed.; John wiley & Sons: New York, 1989; p 986.
16. Clarke, D. J.; Robinson, R. S. *Tetrahedron* **2002**, *58*, 2831.
17. Kaufman, K. D. *J. Org. Chem*. **1961**, *26*, 117.
18. Loutfy, M. *Pharmazie* **1979**, *34*, 672; *Chem. Abstr.* **1980**, *93*, 26221t.
19. Mali, R. S.; Manekar, A. R.; Tilve, S. G. *Indian J. Chem., Sec. B* **1990**, *29B*, 113.
20. Tsai, T. W.; Wang, E. C.; Li, S. R.; Chen, Y. H.; Lin, Y. L.; Wang, Y. F.; Huang, K. S. *J. Chin. Chem. Soc.* **2004** (TW-920268, in press).