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Total synthesis of coriandrin and 7-demethylcoriandrin via a new synthesis of isocoumarins

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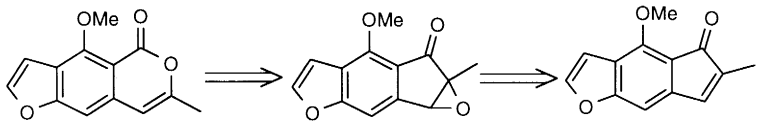
Abstract

Indenone epoxides **8**, prepared from the corresponding indenones, have been shown to undergo clean thermal rearrangement to give isocoumarins **10** in high yields. This synthesis of isocoumarins, when applied to oxaindacenone **7**, resulted in the total synthesis of coriandrin (**1**). © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: coriandrin; isocoumarins; thermal rearrangement; epoxide.

Coriandrin (**1**), one of the two naturally occurring furoisocoumarins known to date, was isolated in 1988 from dry coriander leaves.[1] Its structure was elucidated by extensive analysis of NMR spectra, and confirmed by an X-ray crystallographic study. Structurally quite similar to psoralens (furocoumarins), coriandrin (**1**) exhibits an interesting combination of biological activities. In addition to the expected psoralen activity, it shows in vitro anti-HIV activity.[2] Unlike psoralens, coriandrin (**1**) binds with components of the cell membranes for its biological action. These unique structural and biological characteristics have promoted interest in the synthesis of coriandrin (Scheme 1). Recently, Kraus and Ridgeway reported a nine-step total synthesis of coriandrin (**1**), starting from 5-methylcyclohexane-1,3-dione.[3] A Stille coupling and a Pd(II)-catalyzed pyrone formation were used as the key steps.



1 **6** **7**

Scheme 1.

In a recent study directed towards generation of psoralen analogs, we have demonstrated that oxaindacenone **5** can be readily prepared in three steps from furoate (**2**) in high overall yield (Scheme 2).[4] In view of the close structural resemblance between oxaindacenone **5** and coriandrin (**1**), and rapid

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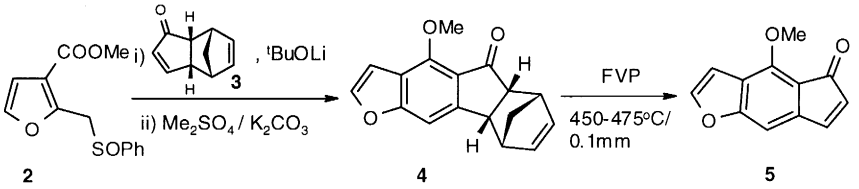
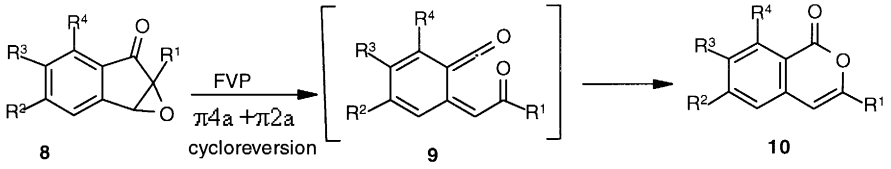
accessibility of indenones by a variety of synthetic routes,[5] we were intrigued by the possibility of the rearrangement of epoxide **6** to **1** (Scheme 1). Although such a rearrangement is not known in the literature, the rearrangement of cyclopentadienone monoepoxides to 2-pyrones, proceeding through an initial thermally allowed [π4a+π2a] cycloreversion has been briefly discussed.[6] However, it has not been examined for the synthesis[7] of isocoumarins or fused isocoumarins, which are of considerable utility as intermediates[8] in the synthesis of natural products. We now report that indenone epoxides **8** can be thermally rearranged to the corresponding isocoumarins **10** in excellent yields, and an application of the rearrangement in the total synthesis of coriandrin (**1**).



Scheme 2.

In order to lay the foundation for the crucial rearrangement, indenone epoxide **8a**, prepared in 76% yield from indenone by epoxidation with H_2O_2/Na_2CO_3 in acetone was submitted to flash vacuum pyrolysis[4] (FVP) (450°C/0.1 mm). The crude pyrolysate after chromatographic purification provided the parent isocoumarin **10a** in 95% yield (Scheme 3). Although the rearrangement required disruption of aromaticity of the benzene ring in **8a** for the initial formation of the ketene aldehyde intermediate **9a**, the outcome of the reaction was as expected. Similarly, the linearly condensed indenone epoxide **8b** was prepared from the corresponding benz[*f*]indenone[9] in 55% yield by treatment with H_2O_2/Et_3N in acetone. When it was pyrolyzed under the above FVP conditions, benzisocoumarin **10b** was obtained in 92% yield. No significant side product was detected. Considering that coriandrin (**1**) has a methyl group at C-7, we then intended to examine the reactivity of the epoxide of 2-methylindenone towards the thermal rearrangement. 2-Methylindenone was prepared by alkylation (LDA, CH_3I) of the cyclo-adduct of indenone and cyclopentadiene, followed by a retro Diels–Alder reaction. The corresponding epoxide **8c** was prepared by treatment with H_2O_2/Et_3N in acetone. Flash vacuum pyrolysis of **8c** furnished 3-methylisocoumarin (**10c**) in 95% yield. Similarly, oxaindacenone **5** was carried forward to 7-demethylcoriandrin (**10d**). Epoxide **8d**, prepared in 75% yield by treatment of **5** with H_2O_2/NaOH, underwent the rearrangement on flash vacuum pyrolysis to give demethylcoriandrin[10] (**10d**) (90%).



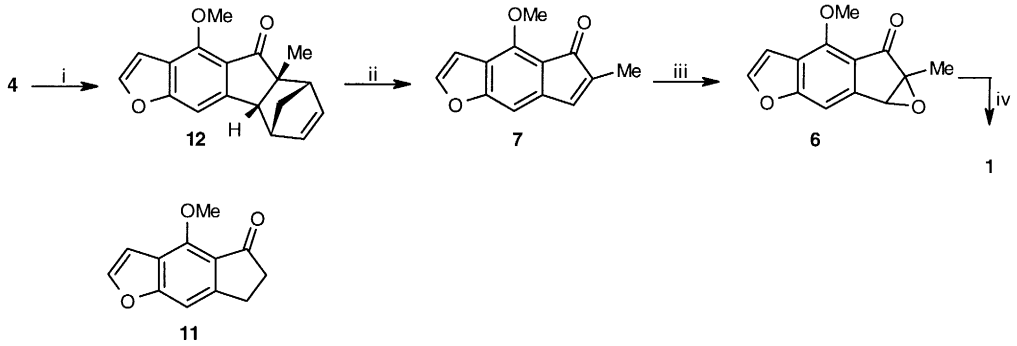
a: $R^1=R^2=R^3=R^4=H$ b: $R^1=H$, $R^2=R^3=CH=CH-CH=CH$, $R^4=H$
c: $R^1=CH_3$, $R^2=R^3=R^4=H$ d: $R^1=H$, $R^2=R^3=O-CH=CH$, $R^4=OMe$

Yields: **10a**; 95%, **10b**; 92%, **10c**; 95%, **10d**; 90%

Scheme 3.

Having successfully worked out model rearrangements of indenone epoxides **8**, we focused our attempts on the preparation of oxaindacenone **7**. Initially, we attempted to utilize **5**, of which Zn–AcOH reduction gave the corresponding 6,7-dihydro product **11** (60%). However, its selective monoalkylation at C-6 was not successful. An alternative route to **7** via monoalkylation of the *N*,*N*-dimethylhydrazone

derivative of **11** was foiled by the fact that the hydrazone could not be prepared. At this point it was decided to make use of the pentacyclic precursor **4**. Treatment of the lithiosalt of **4**, prepared by the action of LDA (1 equiv.), with CH_3I (1 equiv.) furnished **12** in a 50% yield together with 30% of the starting material (Scheme 4). The retro Diels–Alder reaction of **12** at 450°C/0.1 mm furnished **7** (93%) which could be purified by quick silica gel filtration. Epoxidation of **7** by treatment with H_2O_2/Et_3N in acetone gave the epoxide **6**[10] (40%). This was then subjected to FVP to conclude the synthesis of coriandrin (**1**) in 88% yield. The spectral data of the synthetic material were in excellent agreement with those reported for the natural product.



Scheme 4. *Reagents and conditions*: (i) LDA, THF, MeI; (ii) FVP (450–475°C, 0.1 mm); (iii) Et_3N, H_2O_2, acetone; (iv) FVP (450–475°C, 0.1 mm)

In summary, we have introduced a new synthesis of isocoumarins from indenones and achieved a total synthesis of coriandrin. Currently, we are in the process of preparing 2-substituted analogs of coriandrin via lithiation of **12**.

Acknowledgements

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10. Physical data for **10d**: mp 126°C; IR (cm^{-1}) 1721; ^{1}H NMR ($CDCl_3$) δ 7.64 (d, 1H, *J*=2), 7.20 (s, 1H), 7.19 (d, 1H, *J*=5.5), 7.08 (m, 1H), 6.46 (d, 1H, *J*=5.5), 4.23 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.5, 159.1, 157.5, 145.4, 143.4, 135.3, 119.8, 108.4, 107.2, 105.7, 102.5, 61.5. MS (*m/e*) 216 (M^+), 173 (100%). Compound **7**: mp 86°C; IR (cm^{-1}) 1686; ^{1}H NMR ($CDCl_3$) δ 7.43 (d, 1H, *J*=2), 6.95 (m, 1H), 6.84–6.83 (m, 1H), 6.67 (s, 1H), 4.26 (s, 3H), 1.83 (d, 3H, *J*=1.6); ^{13}C NMR ($CDCl_3$) δ 194.7, 159.7, 152.5, 144.0, 143.9, 140.9, 137.6, 119.5, 112.2, 106.7, 101.8, 61.2, 10.2; MS (*m/e*) 214 (M^+, 100%), 199, 185, 171,128. Compound **6**: mp 115–116°C; IR (cm^{-1}) 1711; ^{1}H NMR ($CDCl_3$) δ 7.58 (d, 1H, *J*=2), 7.28 (d, 1H, *J*=1), 6.98 (m, 1H), 4.29 (s, 1H), 4.25 (s, 3H), 1.71 (s, 3H); MS (*m/e*) 230 (M^+), 201 (100%), 187, 159, 144, 129, 116.