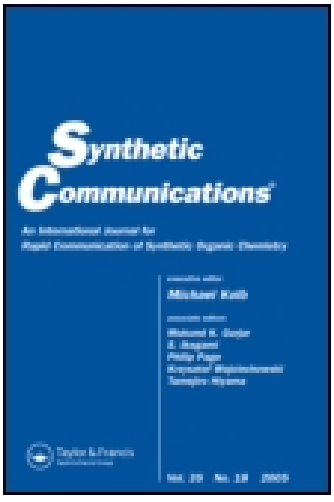


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Short and Efficient Synthesis of Rubrolide E

Subhash P. Chavan [a], Ashok B. Pathak [a], Ankur Pandey [a] & Uttam R. Kalkote [a]

[a] Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune, 411008, India

Published online: 10 Dec 2007.

To cite this article: Subhash P. Chavan, Ashok B. Pathak, Ankur Pandey & Uttam R. Kalkote (2007) Short and Efficient Synthesis of Rubrolide E, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 37:23, 4253-4263, DOI: 10.1080/00397910701575665

To link to this article: http://dx.doi.org/10.1080/00397910701575665

Synthetic Communications®, 37: 4253–4263, 2007

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910701575665

Short and Efficient Synthesis of Rubrolide E

Subhash P. Chavan, Ashok B. Pathak, Ankur Pandey, and Uttam R. Kalkote
Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune, India

Abstract: Short and efficient synthesis of rubrolide E from commercially available 4-methoxyacetophenone, employing ring-closing metathesis, Knoevenagel condensation, and Reformatsky reactions, are the key steps are described.

Keywords: antibiotics, antitumor, epoxide, natural products, total synthesis

INTRODUCTION

Rubrolides **1** (**A**–**F**, **I**–**N**) are the family of biologically active marine ascidian tunicate metabolites. Rubrolides A–F were isolated in 1991 by Miao and Andersen from the colonial tunicate *Ritterella rubra*.[1] They exhibit potent in vitro antibiotic activity and moderate but selective inhibition of protein phosphatases. Rubrolides I–N were isolated in 2000 by Ortega and coworkers from tunicate *Synoicum blochmannii*,[2] which possess significant cytotoxic activity against different kind of cancer cells. Some analogs and related drugs show antitumor properties and biological activity in congestive heart failure and inhibition of cholesterol biosynthesis.[3] A common structural feature of rubrolide is the presence of central butenolide nucleus and two *para*-hydroxyphenyl moieties at the fourth and fifth carbon atom with or without halogen atoms.

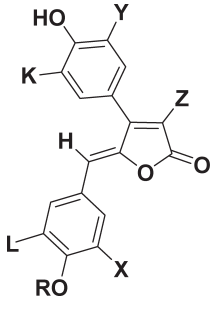
Even though several syntheses of rubrolide and its analogs are reported in the literature,[3a–h] because of its broad spectrum of action against different

Received in India May 8, 2007
Address correspondence to Subhash P. Chavan, Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune 411008, India. E-mail: sp.chavan@ncl.res.in

kinds of diseases and limited supply from natural sources, many organic and medicinal chemists shifted their attention toward the synthesis of this molecule (Figure 1). The first synthesis of rubrolide E was reported by Kotara and Negishi in 1997[3a] involving aromatic halide and coupling with ethynylzinc bromide using Pd (0) as the key step. The literature survey revealed that most of the syntheses start from appropriately substituted formed five-membered heterocyclic moiety (i.e., furanone and maleimide coupling involving Suzuki, Stille, Heck, and Meerwein couplings reactions) and their manipulation into the desired molecules.

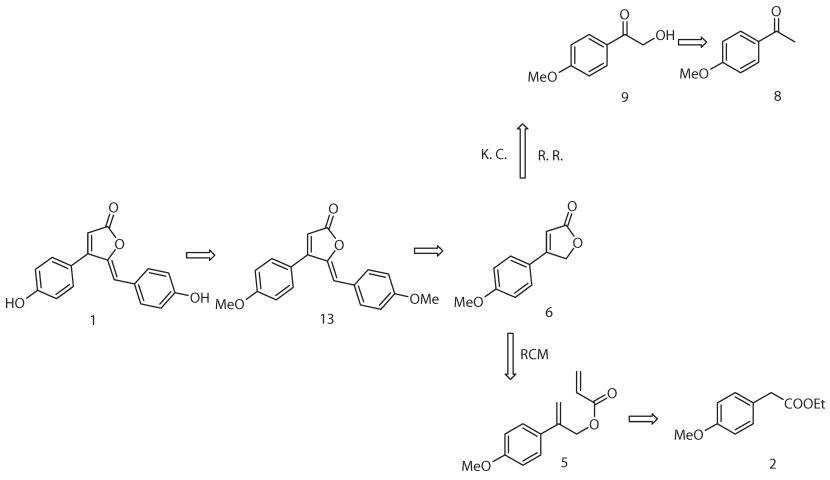
Ring-closing metathesis (RCM) protocol provides a unique entry into cyclic structures, and its usage is increasing in ring construction from small to large size. In connection with an ongoing program in our group on utilization of RCM for the synthesis of biologically active molecules, natural products, and butenolides,[4] we have accomplished the syntheses of a variety of natural products employing RCM as the pivotal step (viz., camptothecin,[4a] microcarpalide,[4b] parvifoline,[4c] and mitralactonine[4d]). Reformatsky reaction is also mild, inexpensive, efficient, facile, and a powerful reaction for the C-C bond formation. Taking advantage of the Reformatsky reaction, we have synthesized naturally occurring compounds, which include butenolides as the end products or intermediates molecules (viz., heritol[5a] mintlactone,[5b] laevigatin,[5c] and lipoic acid[5d]). In keeping with this continued interest, we decided to explore RCM, Reformatsky reaction, and Knoevenagel condensation for the construction of a furanone ring in the synthesis of rubrolide E **1** and some related compounds.

As shown in retrosynthesis (Scheme 1), rubrolide **1** can be readily obtained from arylbutenolide **6** by Knoevenagel condensation and deprotection of methyl groups. The butenolide **6** can be accessed from alcohol **9** by two routes employing Knoevenagel condensation and Reformatsky reaction as the key steps. The alcohol **9** could be accessed from 4-methoxyacetophenone **8**. The butenolide **6** can also be prepared from compound **5** employing RCM as a key step. Compound **5** can be readily obtained from ester **2** as a starting material.



Rubrolide A (1a) R = Z = H; K = L = X = Y = Br
Rubrolide B (1b) R = H; K = L = X = Y = Br; Z = Cl
Rubrolide C (1c) R = K = Y = Z = H; L = X = Br
Rubrolide D (1d) R = L = X = Z = H; K = Y = Br
Rubrolide E (1e) R = L = K = X = Y = Z = H
Rubrolide F (1f) R = Me; L = K = X = Y = Z = H
Rubrolide I (1i) R = K = H; L = X = Y = Br; Z = Cl
Rubrolide J (1j) R = K = Z = H; L = X = y = Br
Rubrolide K (1k) R = K = L = H; X = Y = Br; Z = Cl
Rubrolide L (1l) R = K = Y = H; L = X =Br; Z = Cl
Rubrolide M (1m) R = K = L = Y = H; X = Br; Z = Cl
Rubrolide N (1n) R = K = L = H; Y = Cl; X = Z = Br

Figure 1. Naturally occurring rubrolides.

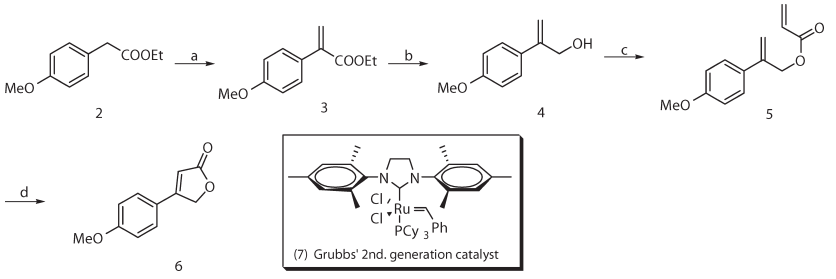


Scheme 1. Retrosynthetic analysis.

Our synthesis commenced from ester **2**, which was prepared from commercially available 4-methoxyphenylacetonitrile by Vogel's procedure. Further treatment of the ester **2** with paraformaldehyde using potassium carbonate as the base and $TBAHSO_4$ as a phase-transfer catalyst gave α,β-unsaturated ester **3** in 89% yield.[6] The reduction of the ester **3** to alcohol was accomplished using diisobutylaluminium hydride (DIBAL-H) at $-78^{\circ}C$ to furnish the corresponding allyl alcohol **4** in 97% yield. The alcohol **4** was reacted with acryloyl chloride using triethyl amine as a base in anhydrous dichloromethane at $0^{\circ}C$ to furnish corresponding ester **5** in 92% yield. Initially, ring-closing metathesis reaction was carried out on compound **5** using Grubbs's first-generation catalyst. Different solvents (viz., dichloromethane, benzene, toluene, and usage of titanium isopropoxide as the Lewis acid) could not render the product at all,[7] whereas Grubbs's second-generation catalyst in anhydrous toluene at $80^{\circ}C$ for 3 days furnished very poor yields of cyclized product in 5–7% yield. This is may be attributed to the quenching of the catalytic cycle by complexation of olefin. Gratifyingly, this problem could be circumvented by addition of titanium isopropoxide as the Lewis acid and by performing RCM in refluxing dichloromethane for 12 h, which furnished butenolide **6**[8] in 83% yield (Scheme 2).

In an another approach involving Knoevenagel condensation, the synthesis started from cheap and commercially available 4-methoxyacetophenone **8**, which was treated with TMSCl to give enol ether, which on treatment with m-chloroperbenzoic acid followed by acid, furnished alcohol **9** in 87% yield over three steps (Scheme 3).

Alcohol **9** was reacted with ethyl malonyl chloride to furnish ester **10** in 97% yield. The Knoevenagel condensation on **10** was accomplished by

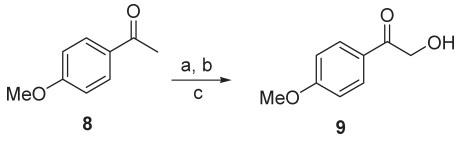


Scheme 2. Reagents and conditions: (a) $(CH_2O)_n$ (1.5 eq.), K_2CO_3 (1.5 eq.), $TBAHSO_4$ (0.1 eq.), toluene, 80°C, 6 h, 89%; (b) DIBAL-H (2.1 eq.), dry DCM, −78°C, 3 h, 97%; (c) Et_3N (1.5 eq.), acryloyl chloride (1.2 eq.), dry DCM, 0°C, 1 h, 92%; (d) **7** (10 mol%), titanium isopropoxide (1.2 eq.), dry DCM, reflux, 12 h, 83%.

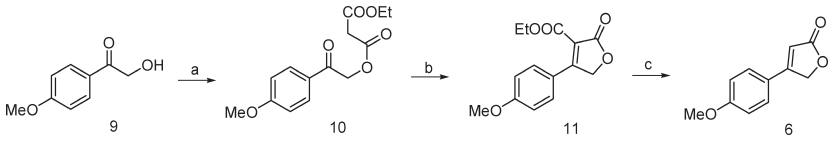
sodium hydride treatment to give α,β-unsaturated lactone **11** in 95% yield. Further decarboxylation under Krapcho's condition afforded the desired butenolide **6** in 91% yield.

After RCM and Knoevenagel condensation reactions employed for the successful synthesis of aryl butenolide **6** (Scheme 4), we thought that **6** could be prepared employing the Reformatsky reaction as a key step. Alcohol **9** was reacted, with ethyl bromoacetate and zinc powder in refluxing benzene–diethyl ether (1:1) to furnish the diol **12**, which was subjected to a catalytic amount of p-toluenesulphonic acid in refluxing benzene to furnish the desired butenolide **6** in 89% yield over two steps.[5d] Still, we felt that both the steps could be performed in one pot. Accordingly, the Reformatsky reaction was carried out under the conditions depicted in Scheme 5 and monitored by thin-layer chromatography (TLC). After the disappearance of the starting material, a catalytic amount of p-toluenesulphonic acid was added, and the reaction mixture was refluxed for additional 3–4 h to afford butenolide **6** in 78% yield. In this way, we achieved tandem three reactions (viz., Reformatsky reaction, dehydration, and lactonization) in one pot in good overall yields.

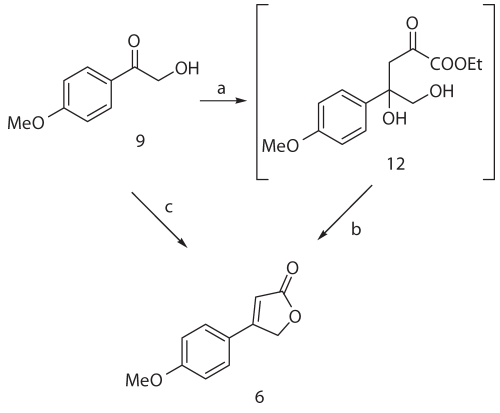
With butenolide **6** by three different strategies in hand, Knoevenagel condensation was carried out with *p*-anisaldehyde, furnishing exclusively (Z)



Scheme 3. Reagents and conditions: (a) Et_3N (2.0 equiv.), TMSCl (1.5 equiv.), dry CH_3CN, reflux, 12 h; (b) 5% $NaHCO_3$ solution (2.0 equiv.), MCPBA (1.2 equiv.), CH_2Cl_2, rt, 3 h; (c) 10% HCl solution (1.5 equiv.), CH_2Cl_2, rt, 12 h, 87% over three steps.



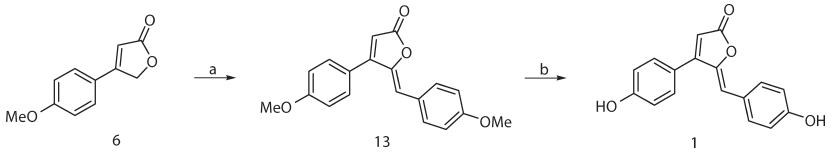
Scheme 4. Reagents and conditions: (a) Et_3N (2.0 equiv.), ethyl malonyl chloride (1.2 equiv.), dry CH_2Cl_2, 0°C, 1 h, 97%; (b) NaH (1.2 equiv.), dry THF, 0°C, 1 h, 95%; (c) NaCl (4.0 equiv.), DMSO-H_2O (3:1), 120–130°C, 6 h, 91%.



Scheme 5. Reagents and conditions: (a) zinc powder (3.0 equiv.), ethyl bromoacetate (1.5 equiv.), C_6H_6–Et_2O (1:1), reflux, 6 h; (b) PTSA (cat.), C_6H_6, reflux, 3 h, 89% over two steps; (c) zinc powder (3.0 equiv.), ethylbromoacetate (1.5 equiv.), C_6H_6–Et_2O (1:1), reflux, 6 h, PTSA (cat.), reflux, 3–4 h, 78%.

butenolide **13** in 81% yield (Scheme 6). Lastly, the demethylation of aromatic methoxy groups using BBr_3 provided the desired rubrolide E **1** in 95% yield. The spectral data of rubrolide E **1** were in good agreement with those reported in the literature.

In conclusion, we have successfully completed a practical, facile, and efficient total synthesis of rubrolide E **1** employing ring-closing metathesis in seven steps with 50% overall yield, Knoevenagel condensation in eight steps with 56%



Scheme 6. Reagents and conditions: (a) piperidine (0.7 equiv.), anisaldehyde (1.0 equiv.), dry MeOH, rt, 81%; (b) BBr_3 (3.0 equiv.), dry CH_2Cl_2, −78°C, 15 min, rt, 24 h, 95%.

overall yield, and Reformatsky reaction in six steps with 52% overall yield and in situ dehydration and lactonization. Also, formal synthesis of rubrolide C was accomplished. The salient feature of the present approach is mild, simple, and high yielding as well as a one-pot version of a three-reaction sequence.

EXPERIMENTAL

All solvents were freshly distilled before use. IR spectra were recorded on a Perkin-Elmer infrared spectrophotometer model 68B or on Perkin-Elmer 1615 FT infrared spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AC-200 (200 MHz). ^{13}C spectra were recorded on a Bruker AC-200 (50 MHz). The carbon spectra were assigned using dimentionless enhanced polarization transfer (DEPT) experiment. Coupling constants (J) were recorded in hertz. Mass spectra were recorded at ionization energy of 70 eV on Finnigan MAT-1020 and on API Q Starpulsar using electron spray ionization (ESI). Microanalytical data were obtained using a Carlo-Erba CHNS-O EA 1108 elemental analyzer. Progress of the reactions were monitored by TLC using Merck silica-gel 60 F_{254} precoated plates, and compounds were visualized by fluorescence quenching, or using iodine, or charring after treatment with the mixture of *p*-anisaldehyd + AcOH + H_2SO_4 in ethanol. Column chromatography was performed using flash silica gel (230 to 400-mesh size).

Ethyl 2-(4-Methoxyphenyl) Acrylate (3)

To a solution of ethyl 2-(4-methoxyphenyl) acetate **2** (5.0 g, 25 mmol) in anhydrous toluene (50 ml), K_2CO_3 (5.37 g, 37 mmol), $TBAHSO_4$ (0.875 g, 2.5 mmol), and $(CH_2O)_n$ (1.125 g, 37 mmol) were added. The reaction mixture was heated at 80°C for 12 h. After completion of the reaction (TLC), H_2O (25 ml) was added and extracted with EtOAc (3 × 25 ml). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash-column chromatography (SiO_2) using 2% EtOAc/pet. ether as eluent, giving 5.3 g of compound **3** as a colorless oil (89% yield). IR ($CHCl_3$): 1716, 1610, 1513, 1251, 1216, 1177, 836 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.33 (t, J = 7.2 Hz, 3H), 3.81 (s, 3H), 4.28 (q, J = 7.2 Hz, 2H), 5.82 (d, J = 1.3 Hz, 1H), 6.25 (d, J = 1.3 Hz, 1H), 6.88 (d, J = 9.0 Hz, 2H), 7.37 (d, J = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 14.0, 55.0, 59.8, 113.3, 124.6, 129.0, 129.3, 140.7, 159.4, 166.9. ESI-MS: m/z 207 ($M^+ + 1$). Anal. calcd. for $C_{12}H_{14}O_3$: 69.88; H, 6.84. Found: C, 69.74; H, 7.02.

2-(4-Methoxyphenyl) Prop-2-en-1-ol (4)

To the solution of ethyl 2-(4-methoxyphenyl) acrylate **3** (3.0 g, 14.5 mmol) in anhydrous CH_2Cl_2 (20 ml) at −78°C, 2 M DIBAL-H (4.34 g, 15.3 ml,

30.5 mmol) was added dropwise. The reaction mixture stirred for 1 h at −78°C, gradually warmed up to room temperature, and further stirred for 2 h. The progress of reaction was monitored by TLC and then reaction was quenched with methanol. The organic layer was separated, and aqueous layer was extracted with CH_2Cl_2 (3 × 15 ml). The combined organic layers were washed with brine solution, dried over anhydrous Na_2SO_4, and filtered, and solvent was removed on a rotary evaporator under reduced pressure. The resulting residue was purified by flash-column chromatography (SiO_2) with EtOAc/pet. ether (2:3) as the eluent to provide compound **4** as a thick colorless oil (2.31 g, 97% yield). IR ($CHCl_3$): 3443, 1609, 1513, 1249, 1216, 1034 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz): δ 3.88 (s, 1H), 4.58 (s, 2H), 5.32 (s, 1H), 5.45 (s, 1H), 6.95 (d, $J = 8.97$ Hz, 2H), 7.46 (d, $J = 8.97$ Hz, 2H). ESI-MS: m/z 165 ($M^+ + 1$). Anal. calcd. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.36. Found: C, 72.91; H, 7.07.

2-(4-Methoxyphenyl) Allyl Acrylate (5)

To the stirred solution of alcohol **4** (2.0 g, 12.19 mmol) in anhydrous CH_2Cl_2 (25 ml), Et_3N (1.85 g, 18.28 mmol) was added at 0°C. The reaction mixture was allowed to stirr for 15 min, and then acryloyl chloride (1.32 g, 14.6 mmol) was added dropwise over 10 min. The reaction mixture was allowed to stir for a further 1 h at 0°C. After the completion of the reaction (TLC), H_2O (20 ml) was added and extracted with CH_2Cl_2 (3 × 15 ml). The combined organic layers were washed with brine (20 ml), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Residue was purified by flash-column chromatography with a mixture of ethyl acetate/pet. ether (1:4) as the eluent to give ester **5** as a viscous colorless liquid (2.44 g, 92% yield). IR ($CHCl_3$): 1721, 1608, 1514, 1215, 758 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 3.83 (s, 3H), 5.05 (d, $J = 1.1$ Hz, 2H), 5.30 (d, $J = 1.1$ Hz, 1H), 5.50 (s, 1H), 5.81–5.87 (dd, $J = 10.2$ & 1.65 Hz, 1H), 6.08–6.22 (dd, $J = 17.2$ & 10.2 Hz, 1H), 6.39–6.48 (dd, $J = 17.2$ & 1.65 Hz, 1H), 6.89 (d, $J = 9.0$ Hz, 2H), 7.40 (d, $J = 9.0$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 55.1, 65.8, 113.5, 113.8, 127.0, 128.2, 130.4, 131.0, 141.6, 159.5, 165.8. MS ESI: m/z 218 (M^+). Anal. calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.48; H, 6.42.

2-Hydroxy-1-(4-Methoxyphenyl) Ethanone (9)

(a) To a stirred solution of 4-methoxyacetophenone **8** (1.0 g, 6.6 mmol) in anhydrous CH_3CN (20 ml), Et_3N (1.34 g, 13.2 mmol) and TMSCl (1.07 g, 9.9 mmol) were added dropwise at room temperature and refluxed for 12 h. The progress of the reaction was monitored (TLC); the reaction mixture was quenched by saturated sodium bicarbonate and extracted with CH_2Cl_2 (3 × 15 ml). The combined organic layers were dried over anhydrous

sodium sulfate and filtered, and solvent was removed under reduced pressure to furnish enol ether as a crude product.

(b) To a stirred solution of crude enol ether (1.48 g, 6.6 mmol) in CH_2Cl_2 (20 ml), 5% $NaHCO_3$ (1.11 g, 13.2 mmol) and MCPBA (1.38 g, 7.92 mmol) were added. The reaction mixture was stirred at room temperature for 3 h. After the disappearance of starting material (TLC), the organic phase was separated, and aqueous phase was extracted with CH_2Cl_2 (3×10 ml). The combined organic layers were dried over anhydrous sodium sulfate, and filtered, and concentrated in vacuo afforded epoxide as a crude product.

(c) To a stirred solution of crude epoxide (1.58 g, 6.6 mmol) in CH_2Cl_2 (10 ml), 10% HCl solution (0.36 g, 3.6 ml, 9.9 mmol) was added, and the reaction mixture was allowed to stir at room temperature for 12 h. The progress of the reaction was monitored by TLC. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×10 ml). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Residue was purified by flash-column chromatography (SiO_2) using ethyl acetate/pet. ether (3:7) as the eluent to furnish hydroxy compound **9** (0.96 g, 87% yield). IR ($CHCl_3$) 3467, 1677, 1602, 1264, 1215, 759, 669 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 3.59 (t, $J = 4.3$ Hz, 1H), 3.89 (s, 3H), 4.82 (d, $J = 3.9$ Hz, 2H), 6.97 (d, $J = 9.0$ Hz, 2H), 7.90 (d, $J = 9.0$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 55.7, 65.1, 114.3, 126.5, 130.15, 164.5, 196.9. ESI-MS: m/z 166 ($M^+ + 1$). Anal. calcd. for $C_9H_{10}O_3$: C, 65.05; H, 06.06. Found: C, 65.19; H, 05.90.

Ethyl 2-(4-Methoxyphenyl)-2-oxoethyl Malonate (10)

To a stirred solution of compound **9** (0.5 g, 3.0 mmol), Et_3N (0.608 g, 6.0 mmol) in CH_2Cl_2 (25 ml) was added. The solution was cooled at 0°C, and ethyl malonyl chloride (0.54 g, 3.6 mmol) was added dropwise at 0°C and stirred for 1 h. After the completion of reaction (TLC), H_2O (50 ml) was added, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×15 ml). Combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Residue was purified by flash-column chromatography using ethyl acetate/pet. ether (1:3) as the eluent to provide ester **10** as a thick colorless oil (0.815 g, 97% yield). IR ($CHCl_3$): 1758, 1736, 1695, 1602, 1264, 1242, 756, 667 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.30 (t, $J = 7.2$ Hz, 3H), 3.57 (s, 2H), 3.88 (s, 3H), 4.24 (q, $J = 7.2$ Hz, 2H), 5.37 (s, 2H), 6.96 (d, $J = 9.0$ Hz, 2H), 7.89 (d, $J = 9.0$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 14.3, 41.4, 55.75, 61.9, 66.7, 114.3, 127.3, 130.3, 164.4, 166.4, 166.5, 190.0. ESI-MS: m/z 280 (M^+). Anal. calcd. for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found: C, 60.11; H, 5.67.

Ethyl 4-(4-Methoxyphenyl)-2-oxo-2,5-dihydrofuran-3-carboxylate (11)

NaH (60%, 0.102 g, 2.57 mmol) was washed by dry pet. ether (10 ml). Dry THF (10 ml) was added and cooled to 0°C. Compound **10** (0.6 g, 2.14 mmol) in THF was added dropwise at 0°C. The reaction mixture was stirred for 1 h at 0°C. After the completion of the reaction (TLC), the reaction mixture was quenched by saturated ammonium chloride solution. Organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 ml). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and filtered, and the solvent was removed on a rotary evaporator under reduced pressure. The resulting crude product was purified by flash-column chromatography using ethyl acetate/pet. ether (1:2) as the eluent, furnishing compound **11** as a pale yellow solid (0.533 g, 95% yield). IR ($CHCl_3$): 1763, 1722, 1606, 1516, 1216, 1038, 758, 668 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 1.35 (t, $J = 7.2$ Hz, 3H), 3.88 (s, 3H), 4.40 (q, $J = 7.2$ Hz, 2H), 5.16 (s, 2H), 6.97 (d, $J = 9.0$ Hz, 2H), 7.55 (d, $J = 9.0$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 47.2, 55.7, 62.0, 70.4, 114.7, 117.15, 121.6, 130.1, 163.0, 163.1, 163.6, 170.25. ESI-MS: m/z 263 ($M^+ + 1$), 285 ($M^+ + 23$). Anal. calcd. for $C_{14}H_{14}O_5$: C, 64.11; H, 5.38. Found: C, 64.19; H, 5.11.

4-(4-Methoxyphenyl) Furan-2-(*5H*)-one (6)

(a) To a solution of allyl acrylate **5** (2.0 g, 9.17 mmol) in anhydrous CH_2Cl_2 (50 ml), titanium isopropoxide (3.12 g, 11.0 mmol) and Grubbs's second-generation catalyst (0.77 g, 0.91 mmol) were added. The reaction mixture was degassed under an argon atmosphere and refluxed for 12 h. After the disappearance of starting material (TLC), the solvent was removed on a rotary evaporator under diminished pressure, and the resultant residue was purified by flash-column chromatography using ethyl acetate/pet. ether (30:70) as eluent, affording the butenolide **6** as a pale yellow solid (1.44 g, 83% yield).

(b) To a solution of ester **11** (0.5 g, 1.9 mmol) in DMSO–H_2O (3:1) (20 ml), NaCl (0.442 g, 7.6 mmol) was added, and the reaction mixture was heated at 120–130°C for 6 h. After the disappearance of starting material (TLC), H_2O (20 ml) was added and extracted with EtOAc (3 × 20 ml). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo, and the residue was purified by flash-column chromatography using the ethyl acetate/pet. ether (30:70) as eluent, affording butenolide **6** as a pale yellow solid (0.329 g, 91% yield).

(c) To a solution of compound **9** (0.5 g, 3.0 mmol) in C_6H_6–Et_2O (1:1) (20 ml), zinc power (0.587 g, 9.0 mmol) and ethylbromoacetate (0.75 g, 4.5 mmol) were added. The reaction mixture was refluxed for 3–4 h, and the progress of the reaction was monitored by TLC. After the disappearance of the starting material, a catalytic amount of PTSA was added and further

refluxed for additional 3 h, monitored by TLC. The reaction mixture was quenched with 10% HCl and extracted with Et_2O (3×10 ml). The combined organic layers were washed with $NaHCO_3$ solution and brine, dried over anhydrous sodium sulfate, filtered, and concentrated under diminished pressure. The residue was purified by flash-column chromatography eluting with (3:7) ethyl acetate/pet. ether, furnishing butenolide **6** as a pale yellow solid (0.446 g, 78% yield). Mp 138°C (lit. 138–139°C). IR ($CHCl_3$): 1745, 1620, 1609, 1514, 1215 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 3.87 (s, 3H), 5.2 (d, $J = 1.6$ Hz, 2H), 6.24 (t, $J = 1.6$ Hz, 1H), 6.97 (d, $J = 9.0$ Hz, 2H), 7.46 (d, $J = 9.0$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 55.4, 70.9, 110.5, 114.6, 122.2, 128.1, 162.3, 163.55, 174.3. ESI-MS: m/z 191 ($M^+ + 1$), 213 ($M^+ + 23$). Anal. calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.38; H, 5.16.

(Z)-5-(4-Methoxybenzylidene)-4-(4-methoxyphenyl) Furan-2(*5H*)-one (13)

To a stirred solution of lactone **6** (1.90 g, 10 mmol) in MeOH, piperidine (595 mg, 7 mmol) and *para*-anisaldehyde (1.36 g, 10 mmol) were added at room temperature, and the mixture was stirred for 15 h. Removal of solvent in vacuo followed by flash-column chromatographic purification of the residue using ethyl acetate/pet. ether (1:9) furnished Z-butenolide **13** as a yellow solid (2.4 g, 78% yield). Mp 136–140°C (lit. 136–140°C). IR ($CHCl_3$): 1754, 1732, 1604, 1511, 1256, 1176, 1032 cm^{-1}. ^1H NMR ($CDCl_3$, 200 MHz) δ: 3.85 (s, 3H), 3.89 (s, 3H), 6.10 (s, 1H), 6.17 (s, 1H), 6.92 (d, $J = 9.0$ Hz, 2H), 7.04 (d, $J = 9.0$ Hz, 2H), 7.46 (d, $J = 8.8$ Hz, 2H), 7.78 (d, $J = 8.8$ Hz, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 55.2, 55.35, 112.1, 113.6, 114.2, 114.4, 122.8, 125.8, 129.9, 132.4, 146.5, 158.3, 160.3, 161.3, 169.2. ESI-MS: m/z 308 ($M^+ + 1$). Anal. calcd. for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found: C, 73.87; H, 5.12.

Rubrolide E (1)

To a stirred solution of **13** (1.54 g, 5 mmol) in anhydrous CH_2Cl_2 (25 ml) at -78°C, a 1 M solution of BBr_3 in CH_2Cl_2 (15 ml, 15 mmol) was added over a period of 15 min. The mixture was then allowed to warm up to room temperature and stirred for a further 24 h. The reaction was quenched with H_2O (25 ml). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3×50 ml). The combined organic layers were washed with H_2O and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue thus obtained was purified by flash silica-gel column chromatography using ethyl acetate/pet. ether (2:3) as the eluant to obtain the natural product rubrolide **1** E as a yellow solid (1.33 g, 95%

yield). Mp 278–281°C (lit. 282–283°C). IR ($CHCl_3$): 3418, 1728, 1604, 1461, 1279, 1170, 830 cm^{-1}. ^1H NMR ($CDCl_3$ + DMSO-d_6, 200 MHz) δ: 6.30 (s, 1H), 6.31 (s, 1H), 6.84 (d, $J = 8.6$ Hz, 2H), 6.93 (d, $J = 8.6$ Hz, 2H), 7.47 (d, $J = 8.6$ Hz, 2H), 7.66 (d, $J = 8.6$ Hz, 2H), 10.33 (bs, 1H), 10.38 (bs, 1H). ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 50 MHz) δ: 111.4, 114.4, 116.7, 116.75, 121.5, 125.0, 131.1, 133.3, 146.1, 158.9, 159.3, 160.3, 169.8. ESI-MS: m/z, 280 (M^+). Anal. calcd. for $C_{17}H_{12}O_4$: C, 72.85; H, 4.32. Found: C, 72.73; H, 4.25.

ACKNOWLEDGMENTS

A. B. P. thanks Council of Scientific and Industrial Research (CSIR), New Delhi, India, for a fellowship, and S. P. C. thanks Department of Science and Technology (DST), New Delhi, India, for funding.

REFERENCES

1. Miao, S.; Andersen, R. J. *J. Org. Chem.* **1991**, *56*, 6275.
2. Ortega, M. J.; Zubia, E.; Ocana, J. M.; Naranjo, S.; Salva, J. *Tetrahedron* **2000**, *56*, 3963.
3. (a) Kotora, M.; Negishi, E. *Synthesis* **1997**, 121; (b) Boukouvalas, J.; Lachance, N.; Ouellet, M.; Trudeau, M. *Tetrahedron Lett.* **1998**, *39*, 7665; (c) Prim, D.; Fuss, A.; Krisch, G.; Silva, A. M. S. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1175; (d) Bellina, F.; Anselmi, C.; Stephane, V.; Mannina, L.; Rossi, R. *Tetrahedron* **2001**, *57*, 9997; (e) Bellina, F.; Anselmi, C.; Rossi, R. *Tetrahedron Lett.* **2002**, *43*, 2023; (f) Bellina, F.; Anselmi, C.; Martina, F.; Rossi, R. *Eur. J. Org. Chem.* **2003**, 2290; (g) Boukouvalas, J.; Pouliot, M. *Synlett* **2005**, 343; (h) Argade, N. P.; Kar, A. *Synthesis* **2005**, *14*, 2284.
4. (a) Chavan, S. P.; Pasupathy, K.; Venkatraman, M. S.; Kale, R. R. *Tetrahedron Lett.* **2004**, *45*, 6879; (b) Chavan, S. P.; Praveen, C. *Tetrahedron Lett.* **2005**, *46*, 1939; (c) Chavan, S. P.; Thakkar, M.; Jogadand, G. F. *J. Org. Chem.* **2006**, *71*, 8986; (d) Chavan, S. P.; Sharma, P. S.; Sivappa, R.; Kalkote, U. R. *Tetrahedron Lett.* **2006**, *47*, 9301.
5. (a) Chavan, S. P.; Zubaidha, P. K.; Dhondge, V. D. *Tetrahedron Lett.* **1992**, *33*, 4605; (b) Chavan, S. P.; Zubaidha, P. K.; Dhondge, V. D. *Tetrahedron* **1993**, *49*, 6429; (c) Chavan, S. P.; Rao, Y. T. S.; Govande, C. A.; Zubaidha, P. K.; Dhondge, V. D. *Tetrahedron Lett.* **1997**, *38*, 6429; (d) Chavan, S. P.; Shivshankar, K.; Pasupathy, K. *Synthesis* **2005**, *8*, 1297.
6. Serelis, A. K.; Simpson, G. W. *Tetrahedron Lett.* **1997**, *38*, 4277.
7. Nakagawa, M.; Arisawa, M.; Theeraladanon, C.; Nishida, A. *Tetrahedron Lett.* **2001**, *42*, 8029.
8. Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651.