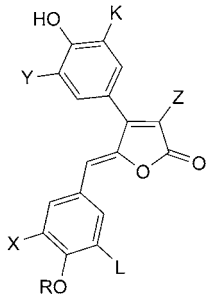
New Concise and Efficient Synthesis of Rubrolides C and E *via* Intramolecular *Wittig* Reaction

by **Nilesh P. Tale**, **Amol V. Shelke**, **Girdharilal B. Tiwari**, **Prerana B. Thorat**, and **Nandkishor N. Karade***

Department of Chemistry, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur, Maharashtra 440033, India
(e-mail: nnkarade@gmail.com)

A short total synthesis of rubrolides C and E has been achieved in four steps, using readily available 4-methoxyacetophenone, 2-bromoacetic acid, and the appropriate aromatic aldehyde, in 46 and 45% yield, respectively. Key reactions involved are α-tosyloxylation of the aryl methyl ketone, intramolecular *Wittig* reaction, *Knoevenagel* condensation, and demethylation.

Introduction. – The γ-benzylidenebutenolide motif with two 4-hydroxyphenyl moieties, with or without halogen atoms, is a common structural feature of a novel family of biologically active marine ascidian metabolites called rubrolides (*Fig.*) [1]. The rubrolides without halogen atoms at C(3) of the butenolide framework are A, C, D, E, and J. The presence of a Cl-atom at C(3) of the furan-2(5*H*)-one is found in the rubrolides B, I, K, L, M, and O, while 3-Br substitution occurs in rubrolide N only. Rubrolides A to H were isolated in 1991 from the colonial tunicate *Ritterella rubra*. It is noteworthy that only minute amounts of rubrolide A (132 mg), B (68 mg), C (48 mg), D (4 mg), E (3 mg), G (8 mg), and H (11 mg) could be obtained from 400 g of the frozen specimens of *Ritterella rubra* after multiple purification steps. The rubrolides are potent non-nitrogenous antibiotics and were also found to possess moderate but selective inhibition of protein phosphatases 1 and 2A. Rubrolides I, K, L, and M have been isolated from the red colonial tunicate *Synoicum blochmanni* and found to display significant cytotoxicities against four different cancer cells lines [2]. Moreover, rubrolide L has recently been shown to be a potent inhibitor of human aldose



Rubrolide A	R = Z = H, K = L = X = Y = Br
Rubrolide B	R = H, K = L = X = Y = Br, Z = Cl
Rubrolide C	R = K = Y = Z = H, L = X = Br
Rubrolide D	R = L = X = Z = H, K = Y = Br
Rubrolide E	R = L = K = X = Y = Z = H
Rubrolide F	R = Me, L = K = X = Y = Z = H
Rubrolide I	R = K = H, L= X = Y = Br, Z = Cl
Rubrolide J	R = K = Z = H, L = X = Y = Br
Rubrolide K	R = K = L = H, X = Y = Br, Z = Cl
Rubrolide L	R = K = Y = H, L = X = Br, Z = Cl
Rubrolide M	R = K = L = Y = H, X = Br, Z = Cl
Rubrolide N	R = K = L = H, Y = Cl, X = Z = Br
Rubrolide O	R = X = H, K = L = Y = Br, Z = Cl

Figure. *Naturally occuring bioactive rubrolides*

reductase, thereby representing a novel lead in the search of new drugs for the treatment of diabetic complications [2a].

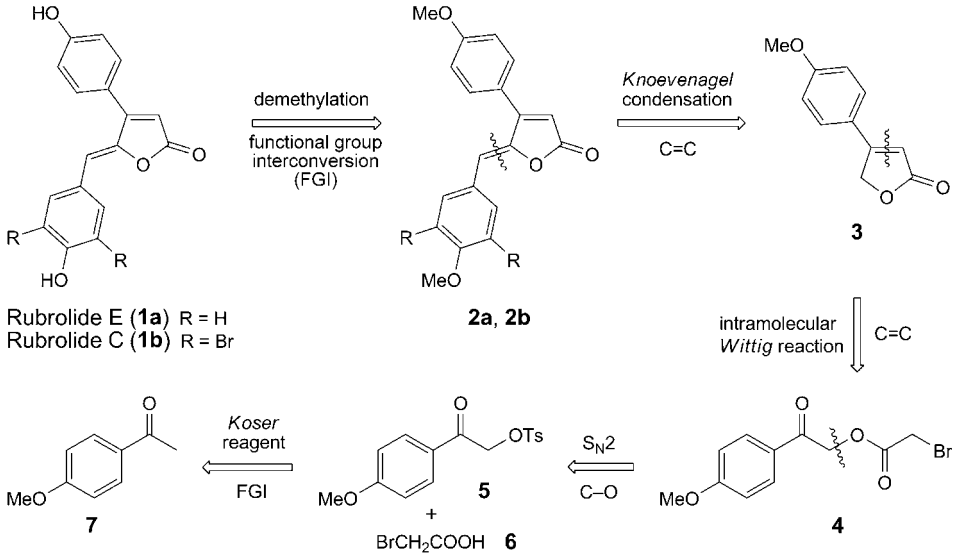
Owing to their useful biological activities and limited supply from the natural source, the rubrolides have attracted considerable attention from the synthesis community. The first synthesis of diacetates of rubrolides A, C, D, and E was reported by *Kotora* and *Negishi* in 1997 by the Pd-catalyzed cross-coupling–lactonization tandem reaction of arylalkyne with β-iodocinnamic acid with $Cl_2Pd(Ph_3P)_2$ and CuI as catalysts [3]. The Pd-catalyzed *Suzuki* cross-coupling reaction between 4-bromo- or 4-tosylfuran-2(5*H*)-one and arylboronic acid has been demonstrated for four step syntheses of rubrolides C and E [4][5]. The requisite 4-bromofuran-2(5*H*)-one was in turn obtained from *Vilsmeier* bromination of β-tetronic acid (=4-hydroxyfuran-2(5*H*)-one), while 4-tosylfuran-2(5*H*)-one was provided by the reaction of TsCl/Et_3N with β-tetronic acid. A six-step synthesis of rubrolide E with 30% overall yield can be achieved by *Meerwein* coupling reaction of 4-anisyldiazonium chloride with *N*-phenylmaleimide as a key step for installation of aryl substituent at C(4) of the furanone ring [6]. Recently, a *Heck* coupling reaction of arenediazonium tetrafluoroborates with 4-hydroxybut-2-enoate in the presence of catalytic amounts of $Pd(OAc)_2$ has been utilized for the synthesis of rubrolide E [7]. Apart from these metal-catalyzed cross-coupling reactions, an eight-step synthesis of rubrolide E has been accomplished from 4-methoxyacetophenone, employing ring-closing metathesis, *Knoevenagel* condensation, and *Reformatsky* reactions [8].

Results and Discussion. – Here, we report a short and efficient synthesis of rubrolide E in four steps with 45% overall yield using readily available starting materials such as 4-methoxyacetophenone, 2-bromoacetic acid, and anisaldehyde. The methodology was also extended to the synthesis of rubrolide C in an overall yield of 46%. Key reactions involved in the synthesis of rubrolides C and E were α-tosyloxylation of aryl methyl ketone, intramolecular *Wittig* reaction, *Knoevenagel* condensation, and demethylation.

The retrosynthetic analysis (*Scheme 1*) for rubrolides C and E reveals that the 4-(4-methoxyphenyl)furan-2(5*H*)-one (**3**) is the common key intermediate which can be constructed *via* intramolecular *Wittig* reaction [9]. The synthesis of rubrolide E, therefore, commenced with the preparation of 2-(4-methoxyphenyl)-2-oxoethyl 2-bromoacetate (**4**). [Hydroxy(tosyloxy)iodo]benzene (HTIB), popularly known as *Koser* reagent, is a versatile hypervalent iodine(III) reagent, used for α-tosyloxylation of enolizable ketones [10]. Because it is generally not necessary to isolate the α-tosyloxy ketone, it is utilized *in situ* as a strategic precursor for the one-pot synthesis of a wide range of α-functionalized ketones [11]. In our study, we have utilized this strategy for the one-pot synthesis of 2-(4-methoxyphenyl)-2-oxoethyl 2-bromoacetate.

Thus, the reaction of 4-methoxyacetophenone with PhI(OH)OTs in refluxing MeCN resulted, in 1.2 h, in the formation of α-tosyloxy-4-methoxyacetophenone (TLC), which was subsequently trapped with 2-bromoacetic acid in the presence of K_2CO_3 to form **4** in 69% yield (*Scheme 2*). The intramolecular *Wittig* reaction of **4** with Ph_3P/Et_3N in THF afforded 4-(4-methoxyphenyl)furan-2(5*H*)-one (**3**) in 89% yield. The *Knoevenagel* condensation of **3** with anisaldehyde by using piperidine as a base in MeOH led exclusively to (5*Z*)-5-(4-methoxybenzylidene)-4-(4-methoxyphenyl)furan-

Scheme 1. *Retrosynthetic Analysis for Rubrolides C and E*



2(5*H*)-one (**2a**) in 79% yield. Finally, **2a** underwent the demethylation reaction with 6 equiv. of BBr_3 in CH_2Cl_2 at $-10°$ to room temperature, by stirring for 4 h, to form rubrolide E (**1a**) in 93% yield. Rubrolide E was thus obtained in four steps in 45% overall yield.

Similarly, the *Knoevenagel* condensation of 3,5-dibromo-4-methoxybenzaldehyde with **3** by using piperidine as a base in MeOH afforded **2b** in 79% yield. Subsequent demethylation of **2b** with BBr_3 resulted in the formation of rubrolide C in 91% yield. Thus, the total synthesis of rubrolide C was accomplished in four steps in a 46% overall yield. All the intermediates involved in the four-step reaction sequence have been well characterized by IR and NMR spectroscopy, and mass spectrometry, and the data obtained are well in agreement with those reported in the literature.

Conclusions. – An efficient and concise four-step synthesis of rubrolide C (four steps; 46% overall yield) and E (four steps; 45% overall yield) has been accomplished from readily available inexpensive starting materials by an intramolecular *Wittig* reaction as a key step for the facile construction of 4-arylfuran-2(5*H*)-one. The possibility of varying the substituents on acetophenones and aromatic aldehydes renderes this methodology as general approach for the synthesis of related compounds.

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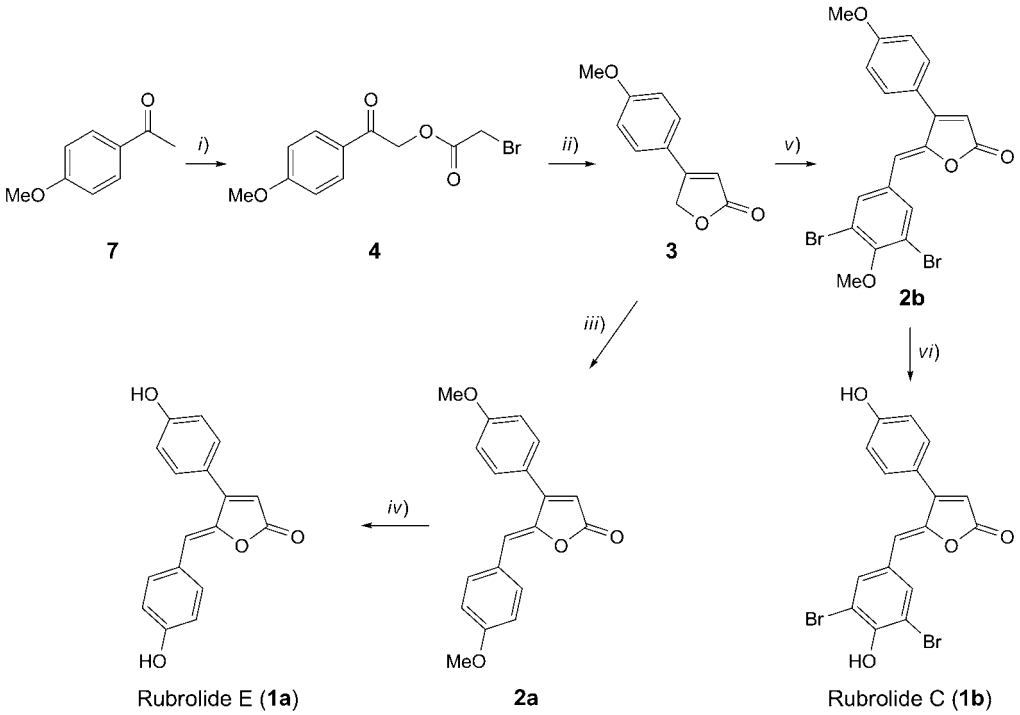
Scheme 2. *Synthesis of Rubrolides C and E*



i) PhI(OH)OTs, MeCN, reflux, 1.2 h, then $BrCH_2COOH/K_2CO_3$ reflux, 4 h; 69%. *ii*) Ph_3P/Et_3N, THF, reflux 2 h; 89%. *iii*) Anisaldehyde, piperidine, MeOH, 15 h, r.t.; 79%. *iv*) Br_3B, dry CH_2Cl_2, $-10°$ to r.t., 24 h; 93%. *v*) 3,5-Dibromo-4-methoxybenzaldehyde, piperidine, MeOH, 15 h, r.t.; 79%. *vi*) Br_3B, dry CH_2Cl_2, $-10°$ to r.t., 24 h; 91%.

Experimental Part

General. All of the org. solvents used were dried on appropriate drying agents and distilled prior to use. All chemicals were commercially available. TLC: *Merck Kieselgel 60 F_{254}*. Column chromatography (CC): silica gel 230–400 mesh. M.p.: Electro thermal melting apparatus; uncorrected. IR Spectra: *Shimadzu FTIR-8300* spectrophotometer; $\tilde{\nu}$ in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra: *Bruker* FT NMR spectrometer operating at 400 and 100 MHz, resp.; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. LC/MS: *Shimadzu 2010*; in *m*/*z*.

Synthesis of 2-(4-Methoxyphenyl)-2-oxoethyl 2-Bromoacetate (**4**) [9b]. To a soln. of 4-methoxyacetophenone (7.5 g, 50 mmol) in MeCN (75 ml) was added [hydroxy(tosyloxy)iodo]benzene (23.52 g, 60 mmol), and the mixture was heated to reflux for 1.5 h. After the successful formation of the α-tosyloxy ketone (as monitored by TLC), $BrCH_2COOH$ (7.64 g, 55 mmol) and K_2CO_3 (8.97 g, 65 mmol) were added, and the mixture was again heated to reflux for 4–5 h until the consumption of α-tosyloxy ketone. After completion of the reaction, the mixture was diluted with H_2O and extracted with AcOEt (70 ml × 2). The org. layer was dried (anh. Na_2SO_4) and concentrated under reduced pressure to give crude product, which was purified by CC (petroleum ether/AcOEt 9:1) to afford pure **4** (9.9 g, 69% yield). M.p. 62–64°. IR (KBr): 1759, 1718, 1686, 1603, 1508, 1425, 1260, 1169, 1026, 929, 944, 773. ^{1}H-NMR ($CDCl_3$): 3.88 (*s*, MeO); 4.03 (*s*, CH_2Br); 5.44 (*s*, CH_2O); 6.95, 7.89 (*AA′BB′*, *J* = 8.8, 4 arom. H). ^{13}C-NMR ($CDCl_3$): 25.33; 55.59; 67.00; 114.23; 126.85; 130.13; 164.25; 166.93; 189.55. ESI-MS: 286.75 ($[M+H]^+$, $C_{11}H_{12}{}^{79}BrO_4^+$; calc. 286.99).

*Synthesis of 4-(4-Methoxyphenyl)furan-2(5*H*)-one* (**3**). To a soln. of **4** (9.6 g, 33.4 mmol) in THF (50 ml), Ph_3P (9.98 g, 37.9 mmol) and Et_3N (5.57 ml, 40.1 mmol) were added, and the mixture was heated to reflux for 2 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, the mixture was concentrated under vacuum, and the residue was purified by CC (petroleum ether/AcOEt 4 : 1) to afford **3** (5.6 g, 89%). Pale yellow solid. M.p. 134 – 136° ([6] 136 – 139°). IR (KBr): 2928, 1735, 1604, 1512, 1425, 1263, 1165, 1047, 895, 835. ^{1}H-NMR ($CDCl_3$): 3.77 (*s*, MeO); 5.09 (*s*, CH_2O); 6.14 (*s*, CH); 6.88 (*d*, $J = 8.9$, 2 arom. H); 7.37 (*d*, $J = 8.9$, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 55.53; 70.98; 110.43; 114.67; 122.19; 128.24; 162.39; 163.71; 174.39. ESI-MS: 190.80 ($[M+H]^+$, $C_{11}H_{11}O_3^+$; calc. 191.07).

*Synthesis of (5*Z*)-5-(4-Methoxybenzylidene)-4-(4-methoxyphenyl)furan-2(5*H*)-one* (**2a**). To a stirred soln. of **3** (2.75 g, 14.4 mmol) in MeOH (20 ml), piperidine (1.42 ml, 14.4 mmol) and 4-anisaldehyde (1.92 ml, 15.9 mmol) were added at r.t., and the mixture was stirred for 15 h. Removal of the solvent *in vacuo* followed by CC (petroleum ether/AcOEt 9 : 1), furnished **2a** (3.52 g, 79% yield). Yellow solid. M.p. 137 – 138° ([6] 136 – 140°). IR (KBr): 2924, 2843, 1763, 1606, 1504, 1427, 1253, 1180, 1020, 922, 823. ^{1}H-NMR ($CDCl_3$): 3.84 (*s*, MeO), 3.88 (*s*, MeO); 6.08 (*s*, CH); 6.15 (*s*, CH); 6.91 (*d*, $J = 8.8$, 2 arom. H); 7.03 (*d*, $J = 8.3$, 2 arom. H); 7.45 (*d*, $J = 8.7$, 2 arom. H); 7.76 (*d*, $J = 8.8$, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 55.41; 55.49; 106.27; 114.40; 114.45; 114.57; 121.25; 125.52; 130.68; 132.69; 146.20; 153.48; 160.75; 161.24; 165.49. ESI-MS: 308.80 ($[M+H]^+$, $C_{19}H_{17}O_4^+$; calc. 309.11).

*Synthesis of (5*Z*)-5-(4-Hydroxybenzylidene)-4-(4-hydroxyphenyl)furan-2(5*H*)-one* (*Rubrolide E*; **1a**). To a stirred soln. of **2a** (3.4 g, 11 mmol) in anh. CH_2Cl_2 (35 ml) at $-10°$, BBr_3 (3.12 ml, 33 mmol) was added dropwise. The resulting mixture was then allowed to warm to r.t. and stirred further for 4 h. The reaction was quenched with NH_4Cl soln. (25 ml). The org. layer was separated, and the aq. layer was extracted with $CHCl_3$ (3 × 50 ml). The combined org. layers were washed with H_2O, dried (anh. Na_2SO_4), filtered, and concentrated *in vacuo*. The residue thus obtained was purified by CC (petroleum ether/AcOEt 4 : 1) to give **1a** (2.8 g, 93%). Yellow solid. M.p. 281 – 282° ([6] 282 – 283°). ^{1}H-NMR (DMSO): 6.06 (*s*, CH); 6.14 (*s*, CH); 6.77 (*d*, $J = 8.72$, 2 arom. H); 6.87 (*d*, $J = 6.8$, 2 arom. H); 7.34 (*d*, $J = 6.8$ Hz, 2 arom. H); 7.59 (*d*, $J = 8.6$, 2 arom. H); 9.71 (*s*, 1 H, ArO*H*); 9.79 (*s*, 1 H, ArO*H*). ^{13}C-NMR (DMSO): 110.49; 113.41; 115.65; 115.75; 120.67; 124.06; 129.82; 132.25; 145.38; 158.21; 158.58; 159.57; 168.56. ESI-MS: 280.90 ($[M+H]^+$, $C_{17}H_{13}O_4^+$; calc. 281.08).

*Synthesis of (5*Z*)-5-(3,5-Dibromo-4-methoxybenzylidene)-4-(4-methoxyphenyl)furan-2(5*H*)-one* (**2b**). To a stirred soln. of **3** (2.75 g, 14.4 mmol) in MeOH (20 ml), piperidine (1.42 ml, 14.4 mmol) and 3,5-dibromo-4-methoxybenzaldehyde (4.67 g, 15.9 mmol) were added at r.t., and the mixture was stirred for 15 h. Removal of the solvent *in vacuo* followed by FC (petroleum ether/AcOEt 4 : 1), furnished **2b** (5.3 g, 79% yield). Yellow solid. M.p. 268 – 270°. IR (KBr): 2926, 2852, 1768, 1608, 1508, 1467, 1251, 1176, 920, 819, 744. ^{1}H-NMR ($CDCl_3$): 3.84 (*s*, MeO); 3.89 (*s*, MeO); 6.01 (*s*, CH); 6.18 (*s*, CH); 7.04 (*d*, $J =$ 6.72, 2 arom. H); 7.44 (*d*, $J = 6.68$, 2 arom. H); 7.94 (*s*, 2 arom. H). ^{13}C-NMR ($CDCl_3$): 55.53; 60.83; 109.90; 113.89; 114.69; 118.52; 130; 134.35; 149.05; 154.69; 158.45; 161.58; 168.47. ESI-MS: 466.90 ($[M+H]^+$, $C_{19}H_{15}{}^{79}Br^{81}BrO_4^+$; calc. 466.93).

*Synthesis of (5*Z*)-5-(3,5-Dibromo-4-hydroxybenzylidene)-4-(4-hydroxyphenyl)furan-2(5*H*)-one* (*Rubrolide C*; **1b**). To a stirred soln. of **2b** (5.1 g, 10.9 mmol) in anh. CH_2Cl_2 (35 ml) at $-10°$, BBr_3 (3.12 ml, 33 mmol) was added dropwise. The resulting mixture was then allowed to warm to r.t. and stirred further for 4 h. The reaction was quenched with NH_4Cl soln. (25 ml). The org. layer was separated, and the aq. layer was extracted with $CHCl_3$ (3 × 50 ml). The combined org. layers were washed with H_2O, dried (anh. Na_2SO_4), filtered, and concentrated *in vacuo*. The residue thus obtained was purified by FC (petroleum ether/AcOEt 9 : 1) to give **1b** (4.3 g, 91%). Yellow solid. M.p. 232 – 234°. ^{1}H-NMR (DMSO): 6.24 (*s*, CH); 6.28 (*s*, CH); 6.87 (*d*, $J = 8.6$, 2 arom. H); 7.40 (*d*, $J = 8.56$, 2 arom. H); 7.95 (*s*, 2 arom. H); 9.73 (*s*, OH); 9.92 (*s*, OH). ^{13}C-NMR (DMSO): 110.01; 111.68; 115.83; 120.17; 127.38; 130.17; 133.96; 147.01; 151.36; 157.89; 159.86; 168.02. ESI-MS: 438.80 ($[M+H]^+$, $C_{17}H_{11}{}^{79}Br^{81}BrO_4^+$; calc. 438.90).

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