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# First total syntheses and absolute configuration of rugulactone and 6(*R*)-(4′-oxopent-2′-enyl)-5,6-dihydro-2*H*-pyran-2-one

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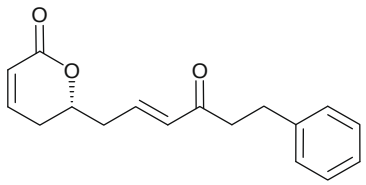
ABSTRACT

The first efficient total syntheses of rugulactone and 6(*R*)-(4′-oxopent-2′-enyl)-5,6-dihydro-2*H*-pyran-2-one have been achieved in six steps with 51% and 48% overall yield, respectively. The key steps are Jacobsen's hydrolytic kinetic resolution (HKR), Horner–Wadsworth–Emmons (HWE) homologation, and ring-closing metathesis reaction.

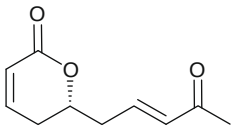


Nuclear factor-κB (NF-κB) is a transcriptional regulator that plays a key role in regulating gene expression by binding to discrete DNA sequences, known as κB elements. NF-κB can exist in homo- and hetero-dimeric forms. NF-κB binds to the target DNA (κB-sites) and initiates gene expressions[1,2] in immunity, stress responses, inflammation, and inhibition of apoptosis.[3–7] Recent studies have shown that the p50 subunit of NF-κB complex is the one that mainly interacts with the HIV-1 long terminal repeat (LTR). Because of these functions, the irregularities, especially the activation of NF-κB has been implicated in many diseases, such as cancer[8–11] and chronic inflammatory diseases.[12,13] Diverse pathways activate NF-κB and control of these pathways is increasingly viewed as an approach to chemotherapy in many diseases that have an associated inflammatory component including cancer, stroke, Alzheimer's disease, and diabetes.[14–22] Although a lot of NF-κB inhibitors has already been reported,[23–25] they share several problems. The strong dependence of HIV gene expression of NF-κB has made it an important and potential drug target. The drugs studied against NF-κB fall mainly into three categories:[26] antioxidant, phosphorylation, and degradation inhibitors and NF-κB-DNA binding inhibitors. The discovery of the role of NF-κB in the regulation of HIV-1 gene expression, Iκκβ inhibition activity has stimulated an intensive search for the inhibitors of NF-κB.

The plant genus *Cryptocarya* is composed of a large number of species distributed throughout the tropics and subtropics.[27] The most common secondary metabolites reported from this genus are alkaloids, flavonoids, and α-pyrones.[28–30] Among them, the 6-substituted 5,6-dihydro-2*H*-pyran-2-ones are structural features of many natural products and display a broad range of biological activities.[31] Rugulactone (**1**) belongs to a family of *Cryptocarya* α-pyrone containing natural products isolated from *Citrus rugulosa* extract that exhibit up to 5-fold induction of Iκκβ at 25 μg/mL.[32] Another similar molecule 6(*R*)-(4′-oxopent-2′-enyl)-5,6-dihydro-2*H*-pyran-2-one (**2**) has been isolated from Piper species (*Piper reticulatum* L.) occurring in Trinidad[33] (Fig. 1).



Rugulactone (**1**)



6(*R*)-(4'-oxopentyl)-5,6-dihydro-2*H*-pyran-2-one (**2**)

**Figure 1.** Structures of rugulactone (**1**) and 6(*R*)-(4′-oxopent-2′-enyl)-5,6-dihydro-2*H*-pyran-2-one (**2**).

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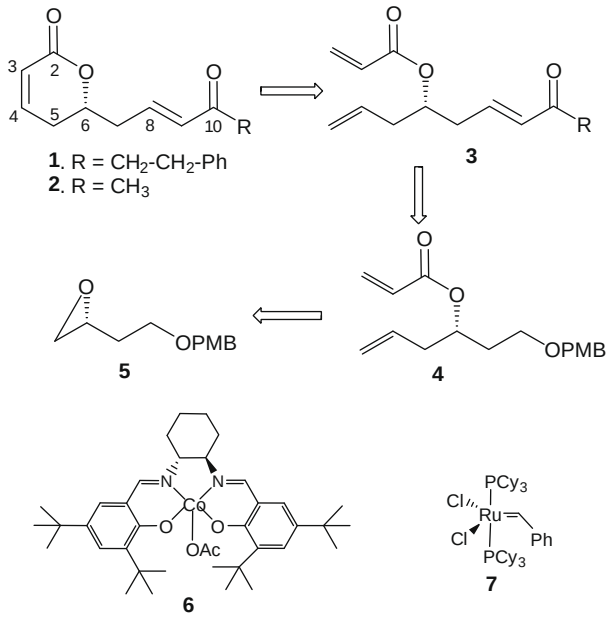
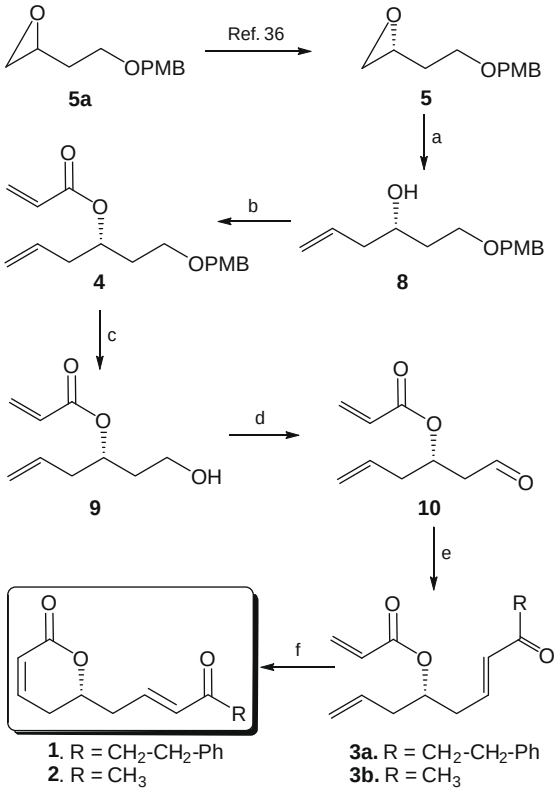
As a part of ongoing program in exploring ring-closing metathesis for bioactive natural lactone synthesis,[34] and with the uncertainty in the proposed structure in mind, we set out to determine the structure of **1** and **2**, including absolute configuration, by means of total syntheses.

The retro-synthesis envisaged based on ring-closing metathesis for the syntheses of **1** and **2** is shown in Scheme 1. As indicated, compound **3** could be obtained from **4** following a Horner–Wadsworth–Emmons reaction, which can be traced back from **5**. For the generation of C6 stereocenter, we relied on Jacobsen's hydrolytic kinetic resolution.

The synthesis of diene **4** began with the epoxide **5**,[35] which in turn was prepared by Jacobsen's hydrolytic kinetic resolution (HKR)[36] of the racemate **5a** (Scheme 2) using (*R*,*R*)-(salen)$Co^{III}$(OAc) catalyst (**6**) to obtain the (*R*)-MPM-ethyl oxirane **5**[37] as a single isomer {$[\alpha]_D^{25}$ +10.6 (*c* 1.2, $CHCl_3$); lit.[35] $[\alpha]_D^{25}$ −10.4 (*c* 1.2, $CHCl_3$); lit.[38] $[\alpha]_D^{25}$ −13.1 (*c* 1.2, $CHCl_3$) for *S*-isomer}. Epoxide **5** was treated with vinyl magnesium bromide in the presence of CuI to afford the homo-allyl alcohol **8** in excellent yield. The spectral and analytical data {$[\alpha]_D^{25}$ −6.2 (*c* 0.6, $CHCl_3$); lit.[39] $[\alpha]_D^{20}$ −5.8 (*c* 1.37, $CHCl_3$) (87% ee)} were in good agreement with the literature values. The C6 stereogenic center was further confirmed by modified Mosher's method.[40] Alcohol **8** was esterified with acryloyl chloride in the presence of $Et_3N$ and a catalytic amount of DMAP to afford the acryloyl ester **4**[41] in 92% yield. With substantial amounts of **4** in hand, we proceeded with the synthesis of **1** and **2**. Thus, deprotection of the PMB group (DDQ, $CH_2Cl_2$, $H_2O$),[42] followed by oxidation of the primary hydroxyl group with Dess–Martin periodinane (DMP)[43] afforded aldehyde **10** in 85.4% yield over two steps. Engagement of the resulting aldehyde **10** in a Horner–Wadsworth–Emmons homologation with dimethyl (2-oxo-4-phenylbutyl) phosphonate[44] in presence of sodium bis(trimethylsilyl)-amide gave the α,β-unsaturated ketone **3a** in 87% yield. Similarly, treatment of aldehyde **10** with dimethyl 2-oxopropylphosphonate in the presence of sodium bis(trimethylsilyl)amide afforded **3b** in 84% yield. Finally, exposure of **3a**[45] and **3b**[46] to Grubbs' first generation catalyst[47] (10 mol %) in refluxing $CH_2Cl_2$ afforded the rugulactone (**1**)[48] and 6(*R*)-(4′-oxopent-2′-enyl)-5,6-dihydro-2*H*-pyran-2-one (**2**)[49] in 82% and 80% yield,




**Scheme 1.** Retrosynthetic analysis of rugulactone (**1**) and 6(*R*)-(4′-oxopent-2′-enyl)-5,6-dihydro-2*H*-pyran-2-one (**2**).




**Scheme 2.** Reagents and conditions: (a) Vinylmagnesium bromide, CuI, THF, 0 °C, 2 h, 91%; (b) acryloyl chloride, $Et_3N$, DMAP, $CH_2Cl_2$, 12 h, 92%; (c) DDQ, $CH_2Cl_2$, $H_2O$, rt, 1 h, 89%; (d) DMP, $CH_2Cl_2$, 0 °C, 2 h, 96%; (e) NaHMDS, phosphonate, 0 °C, 12 h, 87% and 84%; (f) **7**, $CH_2Cl_2$, reflux, 12 h, 82% and 80%.

respectively. The analytical and spectral data (Fig. 2) of our synthetic products were in good agreement with the published data.[32,33]

In conclusion, total syntheses of the natural lactones, rugulactone (**1**) and 6(*R*)-(4′-oxopent-2′-enyl)-5,6-dihydro-2*H*-pyran-2-one (**2**) have been achieved in a highly efficient and concise way utilizing Jacobsen's hydrolytic kinetic resolution, Horner–Wadsworth–Emmons homologation, and ring-closing metathesis as the key reactions. Sizeable amounts of **1** and **2** have thus been made available for further pharmacological studies. Furthermore, applying the same protocol, introduction of variety of truncated side chains and its effects on NF-κB activities are under progress in our laboratory which will be published in due course.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.028.

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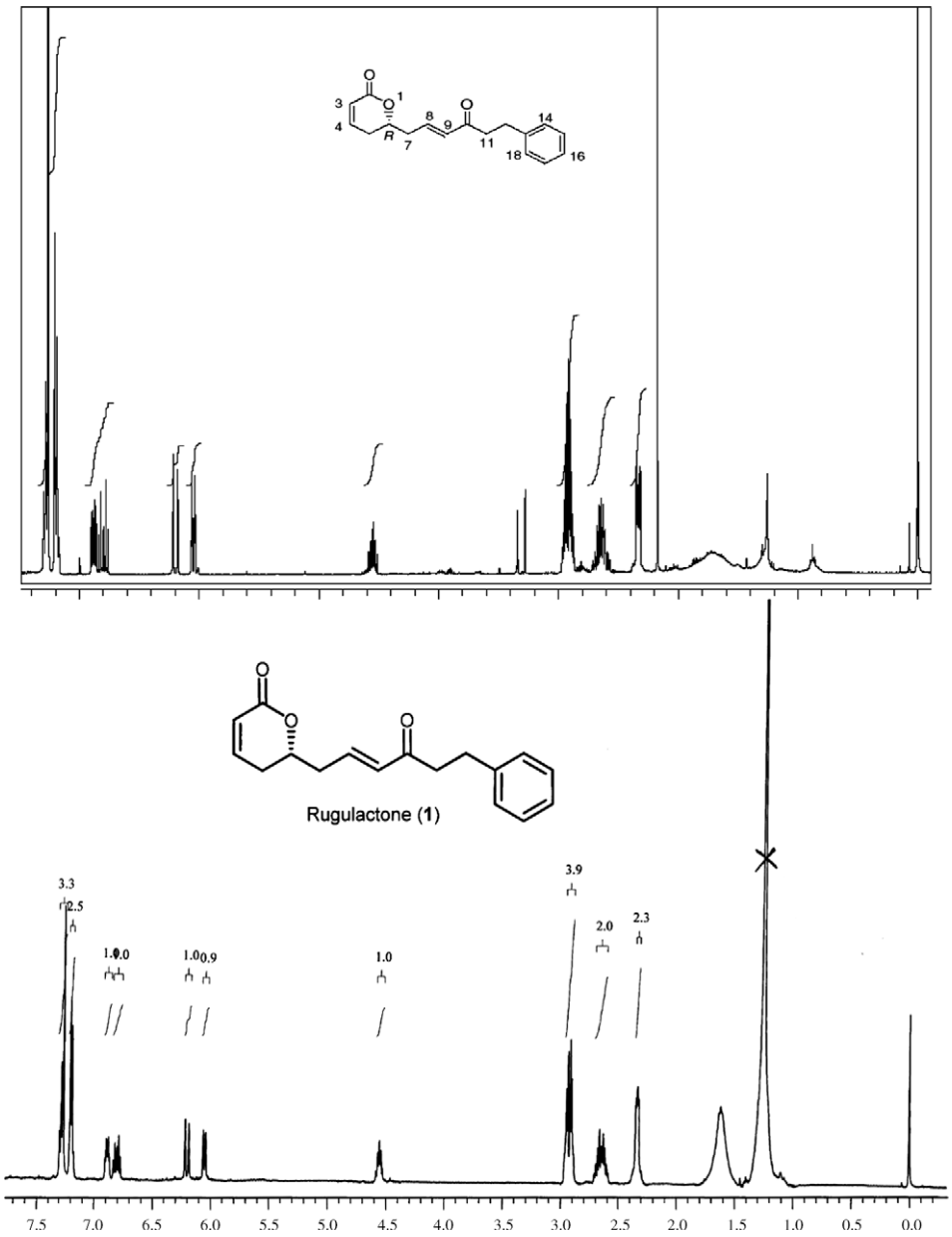


**Figure 2.** $^{1}$H NMR spectra of rugulactone (**1**): natural (top) (500 MHz); and synthetic (bottom) (500 MHz).


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37. *Analytical and spectral data of* **5**: $[\alpha]_D^{25}$ +10.6 (*c* 1.08, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) 7.27 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.46 (s, 2H), 3.80 s, 3H), 3.59 (t, *J* = 7.2 Hz, 2H), 3.06 (m, 1H), 2.78 (t, *J* = 4.7 Hz, 1H), 2.52 (m, 1H), 1.9 (m, 1H), 1.76 (m, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) 159.1, 130.28, 129.2, 113.8, 72.7, 66.7, 55.2, 47.1, 32.9; IR (neat): 3495, 2928, 2857, 1611, 1512, 1247, 1097 $cm^{-1}$; MS (ES+, $3.99 \times 10^6$) *m*/*z* 209 [M+1].
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41. *Analytical and spectral data of* **4**: $[\alpha]_D^{25}$ +20.8 (*c* 0.5, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) 7.19 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 6.35 (m, 2H), 6.07 (m, 1H), 3.78 (s, 3H), 3.54–3.39 (m, 2H), 2.38–2.33 (m, 2H), 1.89–1.83 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$), 165.7, 159.1, 133.3, 130.4, 129.2, 128.6, 117.6, 113.7, 72.7, 70.9, 66.1, 55.2, 38.8, 33.7; IR (neat): 3074, 2928, 2860, 1722, 1613, 1513, 1406, 1248, 1194, 1094, 1039 $cm^{-1}$; MS (ES+, $3.39 \times 10^5$) *m*/*z* 308 $[M+NH_4]^+$, 313 $[M+Na]^+$.
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45. *Analytical and spectral data of* **3a**: $[\alpha]_D^{25}$ −6.0 (*c* 0.3, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) 7.32–7.26 (m, 3H), 7.21–7.18 (m, 2H), 6.74 (m, 1H), 6.39 (dd, *J* = 1.4, 17.2 Hz, 1H), 6.17–6.04 (m, 2H), 5.83 (dd, *J* = 1.2, 10.2 Hz, 1H), 5.74 (m, 1H), 5.14–5.06 (m, 3H), 2.97–2.82 (m, 4H), 2.56–2.47 (m, 2H), 2.37 (t, *J* = 6.6 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) 199.1, 165.5, 141.6, 132.8, 132.7, 131.1, 128.5, 128.3, 126.1, 118.5, 71.7, 41.7, 38.1, 36.5, 30.0, 29.7; IR (neat): 3429, 3028, 2921, 2852, 1723, 1674, 1634, 1406, 1268, 1191, 1048 $cm^{-1}$; MS (ESI+, $2.46 \times 10^5$) *m*/*z* 299 [M+1], 316 $[M+NH_4]^+$, 321 $[M+Na]^+$.
46. *Analytical and spectral data of* **3b**: $[\alpha]_D^{25}$ −7.2 (*c* 0.5, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) 6.73 (m, 1H), 6.40 (d, *J* = 17.2 Hz, 1H), 6.14–6.05 (m, 2H), 5.84 (d, *J* = 10.4 Hz, 1H), 5.75 (m, 1H), 5.14 (d, *J* = 3.9, 2H), 5.10 (s, 1H), 2.58–2.51 (m, 2H), 2.40 (t, *J* = 6.4 Hz, 2H), 2.25 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) 198.2, 165.5, 142.5, 133.2, 132.7, 131.1, 128.3, 118.6, 71.6, 38.2, 36.6, 26.9; IR (neat): 3433, 2924, 2854, 1723, 1676, 1633, 1407, 1262, 1191, 1048 $cm^{-1}$; MS (ES+, $1.76 \times 10^5$) *m*/*z* 231 $[M+Na]^+$.
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48. *Analytical and spectral data of* **1**: $[\alpha]_D^{25}$ −46.5 (*c* 0.7, $CHCl_3$); $^1H$ NMR (500 MHz, $CDCl_3$) 7.28 (m, 3H), 7.20 (m, 2H), 6.88 (ddd, *J* = 3.7, 4.5, 8.9 Hz, 1H), 6.80 (dt, *J* = 7.4, 15.8 Hz, 1H), 6.20 (d, *J* = 15.8, 1H), 6.05 (d, *J* = 9.0 Hz, 1H), 4.55 (q, *J* = 6.8, 13.7 Hz, 1H), 2.93 (m, 2H), 2.91 (m, 2H), 2.64 (m, 2H), 2.33 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) 199.0, 163.7, 144.6, 141.0, 140.0, 133.5, 128.5, 128.4, 126.1, 121.5, 76.1, 41.7, 29.9, 28.9; IR (neat): 3448, 2922, 2852, 1720, 1671, 1632, 1457, 1382, 1247, 1042 $cm^{-1}$; MS (ES+, $1.21 \times 10^6$) *m*/*z* 271 [M+1], 288 $[M+NH_4]^+$, 293 $[M+Na]^+$.
49. *Analytical and spectral data of* **2**: $[\alpha]_D^{25}$ −35.4 (*c* 1.4, $CHCl_3$); $^1H$ NMR (300 MHz, $CDCl_3$) 6.94–6.71 (m, 2H), 6.19 (d, *J* = 16.1, 1H), 6.06 (dt, *J* = 1.7, 9.8 Hz, 1H), 4.62 (m, 1H), 2.71–2.64 (m, 2H), 2.41–2.36 (m, 2H), 2.28 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) 198.1, 163.7, 144.7, 140.8, 134.3, 121.4, 76.1, 37.5, 29.0, 27.0; IR (neat): 3446, 2923, 2853, 1719, 1673, 1631, 1425, 1383, 1248, 1149, 1042 $cm^{-1}$; MS (ES+, $1.05 \times 10^6$) *m*/*z* 181 [M+1], 198 $[M+NH_4]^+$, 203 $[M+Na]^+$.