



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

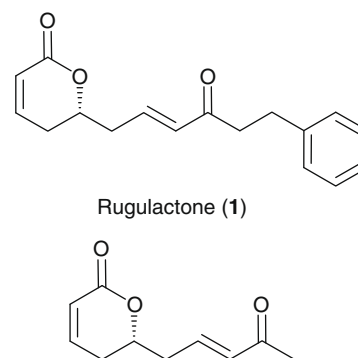
The first efficient total syntheses of rugulactone and 6(*R*)-(4'-oxopent-2'-enyl)-5,6-dihydro-2*H*-pyran-2-one have been achieved in six steps with 51% and 48% overall yield, respectively. The key steps are Jacobsen's hydrolytic kinetic resolution (HKR), Horner–Wadsworth–Emmons (HWE) homologation, and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

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Nuclear factor- κ B (NF- κ B) is a transcriptional regulator that plays a key role in regulating gene expression by binding to discrete DNA sequences, known as κ B elements. NF- κ B can exist in homo- and hetero-dimeric forms. NF- κ B binds to the target DNA (κ B-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- κ B 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- κ B has been implicated in many diseases, such as cancer^{8–11} and chronic inflammatory diseases.^{12,13} Diverse pathways activate NF- κ B 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- κ B inhibitors has already been reported,^{23–25} they share several problems. The strong dependence of HIV gene expression of NF- κ B has made it an important and potential drug target. The drugs studied against NF- κ B fall mainly into three categories:²⁶ antioxidant, phosphorylation, and degradation inhibitors and NF- κ B-DNA binding inhibitors. The discovery of the role of NF- κ B in the regulation of HIV-1 gene expression, I κ B inhibition activity has stimulated an intensive search for the inhibitors of NF- κ B.

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 I κ B at 25 μ g/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 Trinidad³³ (Fig. 1).



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

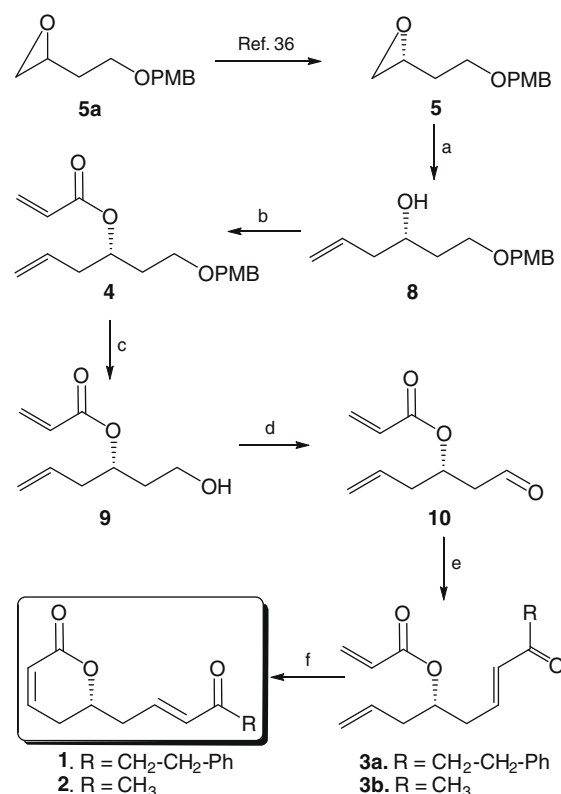
Figure 1. Structures of rugulactone (**1**) and 6(*R*)-(4'-oxopent-2'-enyl)-5,6-dihydro-2*H*-pyran-2-one (**2**).

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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, CHCl₃); lit.³⁵ $[\alpha]_D^{25} -10.4$ (c 1.2, CHCl₃); lit.³⁸ $[\alpha]_D^{25} -13.1$ (c 1.2, CHCl₃) 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, CHCl₃); lit.³⁹ $[\alpha]_D^{20} -5.8$ (c 1.37, CHCl₃) (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 Et₃N 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, CH₂Cl₂, H₂O),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) phosphonate⁴⁴ 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 catalyst⁴⁷ (10 mol %) in refluxing CH₂Cl₂ 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 2. Reagents and conditions: (a) Vinylmagnesium bromide, CuI, THF, 0 °C, 2 h, 91%; (b) acryloyl chloride, Et₃N, DMAP, CH₂Cl₂, 12 h, 92%; (c) DDQ, CH₂Cl₂, H₂O, rt, 1 h, 89%; (d) DMP, CH₂Cl₂, 0 °C, 2 h, 96%; (e) NaHMDS, phosphonate, 0 °C, 12 h, 87% and 84%; (f) **7**, CH₂Cl₂, 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- κ B activities are under progress in our laboratory which will be published in due course.

Acknowledgment

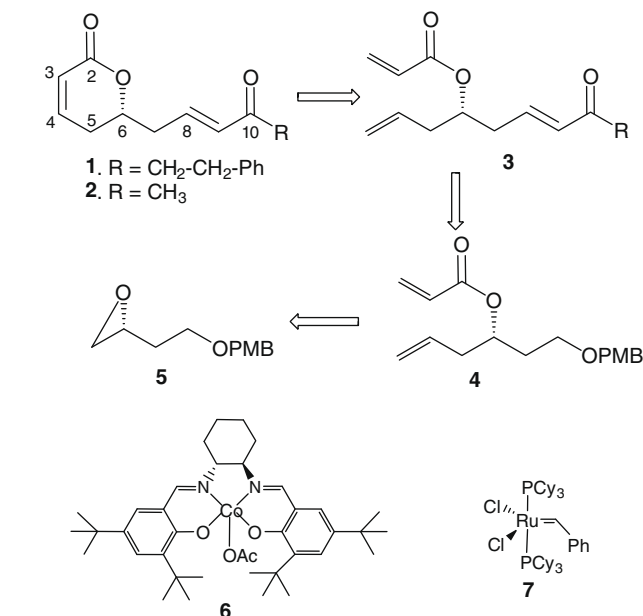
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Supplementary data

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

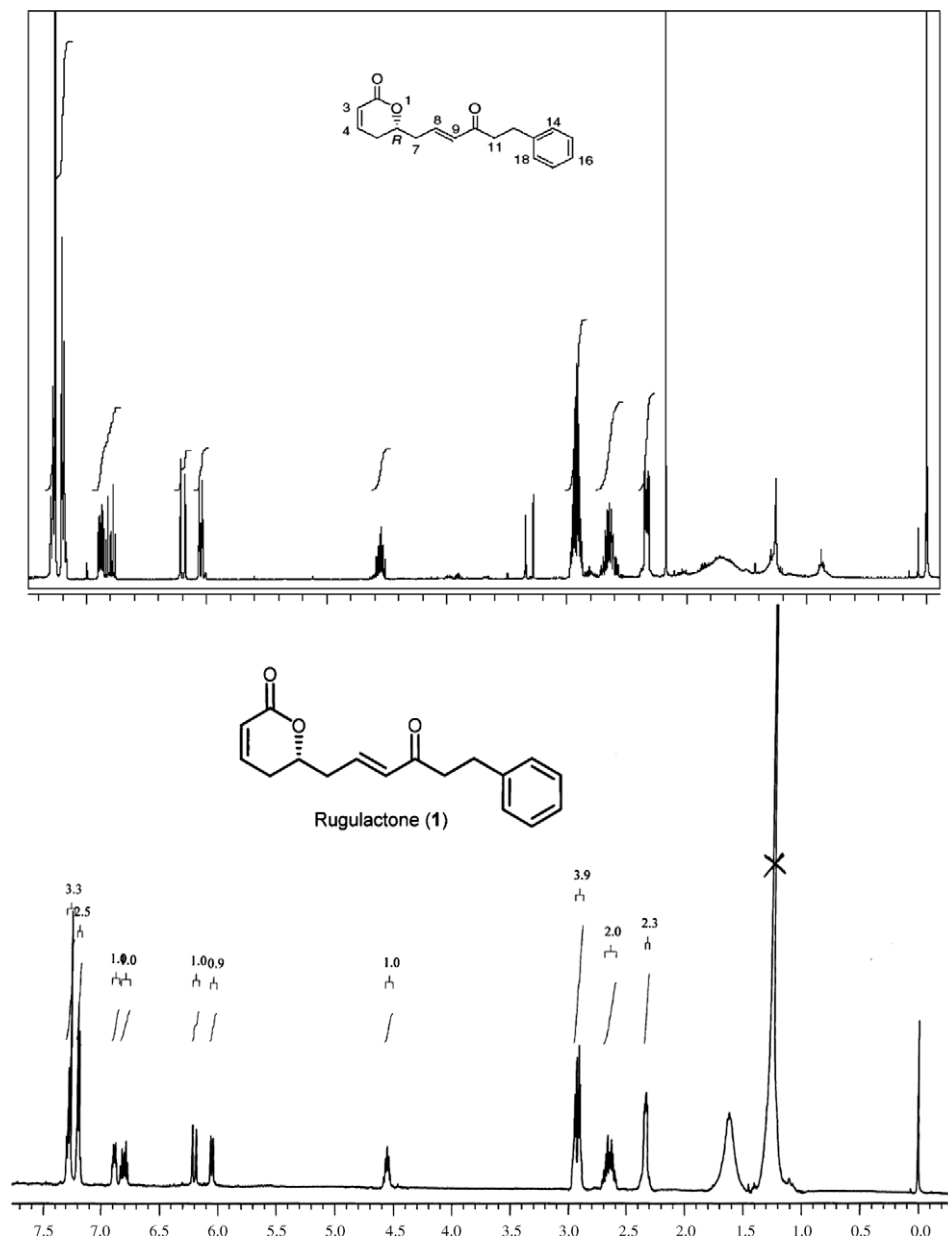


Figure 2. ^1H NMR spectra of rugulactone (1): natural (top) (500 MHz); and synthetic (bottom) (500 MHz).

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37. *Analytical and spectral data of 5*: $[\alpha]_D^{25} +10.6$ (c 1.08, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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⁺, 3.99×10^6) *m/z* 209 [M+1].
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45. *Analytical and spectral data of 3a*: $[\alpha]_D^{25} -6.0$ (c 0.3, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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⁺, 2.46×10^5) *m/z* 299 [M+1], 316 [M+NH₄]⁺, 321 [M+Na]⁺.
46. *Analytical and spectral data of 3b*: $[\alpha]_D^{25} -7.2$ (c 0.5, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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⁺, 1.76×10^5) *m/z* 231 [M+Na]⁺.
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49. *Analytical and spectral data of 2*: $[\alpha]_D^{25} -35.4$ (c 1.4, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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⁺, 1.05×10^6) *m/z* 181 [M+1], 198 [M+NH₄]⁺, 203 [M+Na]⁺.