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An expedient enyne metathesis approach to dysidiolide

Krishna P. Kaliappan* and Parthasarathy Gowrisankar

Department of Chemistry, Indian Institute of Technology—Bombay, Powai, Mumbai 400 076, India

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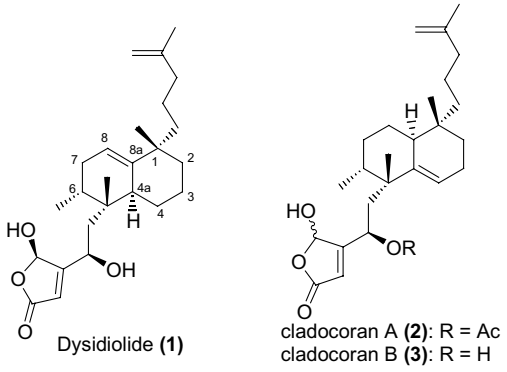
Dedicated to Professor S. Chandrasekaran on the occasion of his 60th birthday

Abstract—A short and efficient enyne metathesis route is reported for the construction of a key intermediate required in the synthesis of dysidiolide thus completing its formal synthesis.

In 1996, Gunasekara et al. reported[1] the isolation of a structurally novel neo-isolabdanoid sesterterpene, dysidiolide **1**, from the Caribbean marine sponge *Dysidea etheria de Laubenfels*, which was collected off the Bahamian islands. Its unusual structure and relative configuration was elucidated by single crystal X-ray diffraction crystallography. Soon, two more structurally related novel sesterterpenes, cladocorans A and B were isolated[2] by Fontana et al. from the Mediterranean coral *Cladocora cespitosa*. Dysidiolide has been shown to inhibit the growth of A-549 human lung carcinoma ($IC_{50} = 4.7\,\mu M$) and P388 murine leukemia cells ($IC_{50} = 1.5\,\mu M$). Furthermore, this is the first natural product discovered thus far to inhibit protein phosphatase cdc25A ($IC_{50} = 9.4\,\mu M$). Though the biological activity of cladocorans has not yet been reported, it is likely that they will also inhibit protein phosphatase and phospholipase A_2 in view of their structural similarity with dysidiolide.[3] Dysidiolide also possesses a unique molecular architecture with a hydrophobic bicyclo[4.4.0]decane structural subunit having an unprecedented side chain in the top half and a hydrophilic γ-hydroxybutenolide in the bottom. Interestingly, the hydrophobic and hydrophilic side chains are in close proximity.



Owing to its unique properties, several total syntheses,[4] formal syntheses,[5] and approaches[6] toward **1** have been reported. There are also a few reports[7] on structure–activity relationships (SAR) and it has been shown that some unnatural diastereomers of **1** are more potent than the natural compound. Recently, Waldmann's group reported[8] a combinatorial synthesis of several analogues of dysidiolide and observed that the core structure of dysidiolide is essential for biological activity. However, facile access to potent analogues remains a challenge as existing syntheses have limitations due to multi-step processes. Herein, we report a short and efficient enyne metathesis route[9] to a key intermediate required for the synthesis of dysidiolide.

All the reported synthetic approaches to total syntheses of dysidiolide start from a cyclic precursor; our synthetic strategy differs in that it starts from an acyclic precursor (Scheme 1). Retrosynthetically, an access to the key bicyclic intermediate **4**, which has been converted[4a,b,8] into dysidiolide, was envisaged by an intramolecular enyne metathesis reaction from **5**. The enyne **5** could be easily obtained from the nitrile **6** in a few steps, which, in turn, could be obtained from propionitrile **7** by successive alkylation with electrophiles **8** and **9**.

Keywords: Dysidiolide; Grubbs' catalyst; Enyne metathesis; Formal synthesis; Anticancer.
* Corresponding author. Tel.: +91 22 576 7177; fax: +91 22 572 3480; e-mail: kpk@iitb.ac.in

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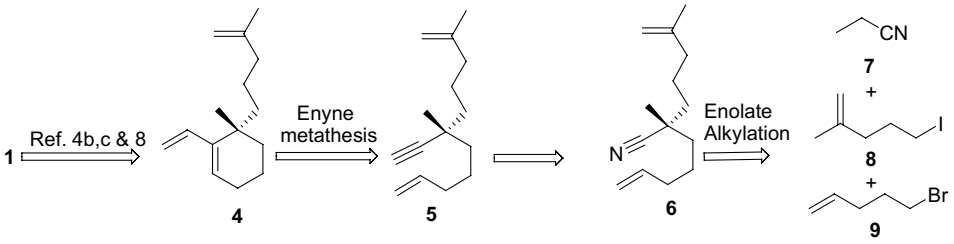
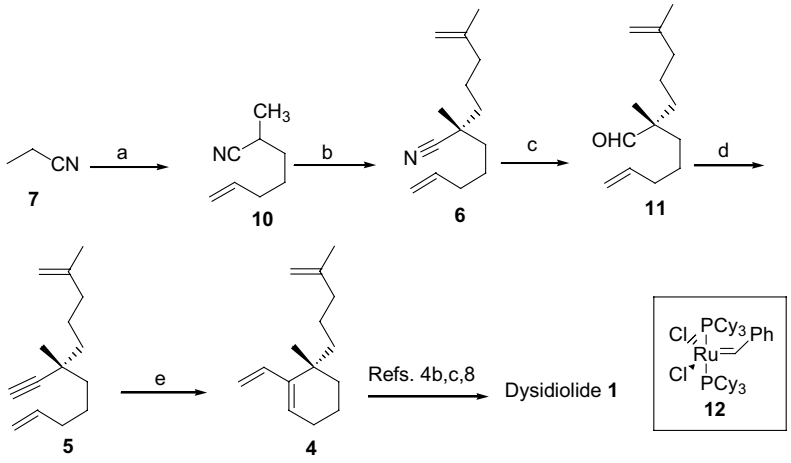


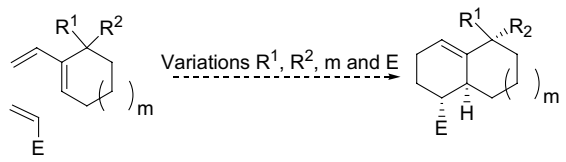
Scheme 1.



Scheme 2. Reagents and conditions: (a) LDA, THF, −78 °C, 2 h, add **9**, then rt, 16 h, 44%; (b) LiHMDS, THF, **8**, rt, 1.5 h, 95%; (c) DIBAL-H, THF, −78 °C to rt, 51%; (d) $CH_3COC(N_2)PO(OEt)_2/K_2CO_3$/MeOH, rt, 5 h, 75%; (e) Grubbs' catalyst **12** (10 mol%), DCM, reflux, 2 h, 85%.

The synthetic sequence starting from propionitrile **7** is outlined in Scheme 2. Alkylation of **7** with 5-bromopentene was successfully achieved with LDA as base in moderate yield. The second alkylation with the known[10] iodo compound **8** was more facile with LiHMDS as base and the product **6** was isolated in excellent yield. Partial reduction of the cyano group with DIBAL-H followed by conversion of the aldehyde into an alkyne following Bestmann's protocol[11] afforded the enyne precursor **5**. Then key enyne metathesis was carried out under standard dilute conditions with the Grubbs' first generation catalyst **12** to afford the diene **4**.[12] The spectral data of **4** match those reported[4,8] in all aspects thus completing a short and efficient formal synthesis of dysidiolide.

In summary, we have developed a concise and efficient route to a key intermediate **4** in the total synthesis of dysidiolide. The salient features of this synthesis are successive alkylations of a nitrile with different electrophiles and an efficient enyne metathesis. Using this highly convergent strategy, it should be possible to make a range of dysidiolide analogues with at least four variations as shown in Scheme 3. Efforts are underway in our laboratory to synthesize several simpler analogues of dysidiolide.



Scheme 3.

Acknowledgements

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References and notes

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12. All compounds reported here were duly characterized. Selected data: For **10**: $R_f = 0.35$ [silica gel, ethyl acetate:hexane (1:20)], IR (neat) 2983, 2941, 2863, 2236, 1728, 1643, 1461, 1385, 1001, 915 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.85–5.72 (m, 1H), 5.07–4.97 (m, 2H), 2.65–2.58 (m, 1H), 2.14–2.07 (m, 2H), 1.68–1.49 (m, 4H), 1.32 (d, $J = 7.3$, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.8, 123.1, 115.4, 33.4, 33.1, 26.2, 25.5, 18.1. For **6**: $R_f = 0.38$ [silica gel, ethyl acetate:hexane (1:20)], IR (neat) 2979, 2942, 2866, 2233, 1731, 1649, 1462, 1377, 993, 890 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.86–5.72 (m, 1H), 5.07–4.97 (m, 2H), 4.74–4.69 (m, 2H), 2.17–2.0 (m, 4H), 1.72 (s, 3H), 1.69–1.33 (m, 8H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.9, 137.9, 124.5, 115.3, 110.6, 38.9, 38.9, 37.6, 36.6, 33.6, 24.1, 24.0, 22.6, 22.3. For **5**: $R_f = 0.7$ [silica gel, hexane], IR (neat) 2970, 2941, 2868, 2108, 1649, 1461, 1375, 992, 911, 988 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.89–5.75 (m, 1H), 5.06–4.93 (m, 2H), 4.69 (d, $J = 5.3$ Hz, 2H), 2.09–1.99 (m, 4H), 1.72 (s, 3H), 1.63–1.27 (m, 9H), 1.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.9, 138.9, 114.6, 110.1, 91.0, 68.9, 41.1, 41, 38.2, 34.7, 34.2, 26.5, 24.2, 22.7, 22.4. For **4**: $R_f = 0.76$ [silica gel, hexane], IR (neat) 2936, 2868, 1649, 1456, 1374, 987, 905, 887 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.27 (ddd, $J = 12.1$, 11.0, 1.1 Hz, 1H), 5.84 (t, $J = 4.1$, 1H), 5.27 (dd, $J = 17.2$, 1.8 Hz, 1H), 4.90 (dd, $J = 12.8$, 1.8 Hz, 1H), 4.67(d, $J = 7.3$ Hz, 2H), 2.05–1.93 (m, 4H), 1.69 (s, 3H), 1.67–1.26 (m, 8H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 146.2, 143.9, 137.2, 124.2, 112.8, 109.8, 40.2, 38.7, 36.3, 35.1, 27.0, 26.2, 22.4, 22.0, 19.1; HRMS (ES) calcd. for $C_{15}H_{24}$ (M+1) 205.1956, found (M+1) 205.1965.