First total synthesis of yanuthones: novel farnesylated epoxycyclohexenoid marine natural products

Goverdhan Mehta* and Subhas Chandra Pan

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

Abstract—The total synthesis of the recently isolated marine natural products of mixed biosynthetic origin, yanuthones A, B, C and 22-deacylyanuthone A, has been accomplished following a short regio- and stereocontrolled approach involving the key intermediary of 2-farnesyl-p-benzoquinone.

Hybrid natural products derived through mixed biosynthetic pathways evoke intrinsic synthetic interest as they embody diverse structural fragments.1 In the year 2000, Ireland and co-workers2 reported the isolation and structure elucidation of eight bioactive farnesylated epoxycyclohexenoids 1–8 with various oxy-substitution patterns from an Aspergillus niger isolate obtained from tissue homogenates of an orange Aplidium sp. ascidian. These natural products were named yanuthones A–E, and derivatives, as shown in Chart 1. They exhibited weak antimicrobial activity against methicillin resistant Staphylococcus aureus and vancomycin resistant Enterococcus. More recently, deacetoxyyanuthone A 9, a close congener of 1–8, along with other related compounds has been isolated from a marine isolate of genus Penicillium sp. and shown to display mild antibacterial activity against methicillin resistant and multidrug resistant S. aureus (MIC, 50 μg/ml).3

There have also been earlier literature reports of the isolation of farnesylated epoxycyclohexenoid natural products derived through the combination of the shikimate and mevalonate pathways.2–5 For example, the research groups of Anke and co-workers4 and Rickards and co-workers5 have reported the structure elucidation of the oligosporon group of antibiotics, for example, oligosporon 10 and oligosporol B 11 (Chart 1) from the culture strains of Arthrobotrys oligospora from Netherlands and Australian isolates, respectively. It was further shown that the oligosporon group of natural products exhibit antibacterial, cytotoxic and nematocidal effects. The structural uniqueness of these farnesylated epoxyquinone natural products coupled with their diverse occurrence and wide ranging bioactivity profile aroused our synthetic interest. In this letter, we disclose a simple and general strategy that has resulted in the first total synthesis of several yanuthones in racemic form.

In formulating a general synthetic approach to yanuthones and other farnesylated epoxycyclohexenoid natural products, Chart 1, we recognized the pivotal role of 2-farnesyl-p-benzoquinone 12 as the starting point. Quite surprisingly, while 12 has been found in Nature,6 its synthesis, to our knowledge, has only been reported once.7a There is also a report in the patent literature7b following a somewhat circuitous route. Our initial engagement therefore was to devise a convenient access to 12 from readily available starting materials and this objective was achieved following Yamamoto’s recent adaptation8a of a previously described protocol8b for the direct dehydrative coupling between polyprenyl alcohols and phenols. Thus, when a mixture of commercially available p-methoxyphenol 13 and (E,E)-farnesol 14 was exposed to scandium(III) triflate (30 mol %), 2-farnesylhydroquinone monomethyl ether 15 was obtained (Scheme 1). Ceric ammonium nitrate (CAN) oxidation of 15 delivered the key 2-farnesyl-p-benzoquinone 12 precursor smoothly and in just two steps (Scheme 1).

The next task was to elaborate the quinone moiety present in 12 to the requisite epoxy-cyclohexenoid functional array present in yanuthones 1–8, in a stereocontrolled
manner. For this purpose, a tactic recently highlighted by us in the syntheses of several epoxyquinone natural products was adopted. Thus, Diels–Alder reaction of 2-farnesyl-p-quinone with cyclopentadiene was regio- and stereoselective and furnished the endo-adduct in good yield (Scheme 1). Base-mediated epoxidation on the enedione moiety in topologically biased occurred as anticipated from the convex face to furnish exclusively the exo-epoxyquinone derivative. DBU-mediated hydroxymethylation of was stereoselective (exo-face preference) and regioselective (10:1) with predominant C–C bond formation with respect to the farnesyl chain to furnish hydroxymethyl dione. At this stage, a quick check was made on the efficacy of our strategy by subjecting the tri cyclic dione to retro-Diels–Alder reaction to furnish enedione, acet ylation of which led to whose spectral data were found to be identical with those reported for the natural product yanuthone B (Scheme 1).

Encouraged by this convenient access to the natural product yanuthone B, we ventured to extend our strategy to other yanuthones, which besides other functional group adjustments required installation of the requisite hydroxyl group stereochemistry at C-15 corresponding to the natural products. Taking a cue from our recent contra-intuitive observation, the tricyclic hydroxy-dione was subjected to DIBAL-H reduction, employing two equivalents of the reagent, to furnish the exo-hydroxy product in a remarkable regio- and stereocontrolled operation (Scheme 2). The opposite stereochemical outcome during the DIBAL-H reduction of monocyclic underscores the importance of tight stereoelectronic control, engendered by the vicinal environment for aluminium coordination, in these reductions. Carefully controlled acetylation of furnished a mixture of epi-yanuthone A  and epi-yanuthone C (2:1). The coupling constants in the epi-series were

The relative stereochemistry of the yanuthones and other compounds displayed in Chart 1, particularly the C-15 hydroxyl stereochemistry, has been primarily assigned on the basis of the J H-14,H-15 coupling constants, which typically were found to be in the range of 2.5–3.0 Hz for the cis-stereochemic disposition. While comparison of these J values was made with some model epoxycyclohexenones having a cis-disposition, the coupling constant data for the corresponding compounds with H-14 and H-15 in a trans-relationship were not available. We therefore decided to further secure the stereochemical assignment of the C-15 hydroxyl in the yanuthones by preparing the C-15 epimers of yanuthones for comparison purposes.

Towards this end, endione was reduced with Dibal-H to furnish 22-deacetyl-epi-yanuthone A in a regio- and stereocontrolled reduction (Scheme 3). The opposite stereochemical outcome during the DIBAL-H reduction of monocyclic underscores the importance of tight stereoelectronic control, engendered by the vicinal environment for aluminium coordination, in these reductions. Carefully controlled acetylation of furnished a mixture of epi-yanuthone A and epi-yanuthone C (2:1). The coupling constants in the epi-series were
Scheme 1. Reagents and conditions: (a) \((E,E)\)-farnesol 14, Sc(OTf)\(_3\) (30 mol %), toluene, 0–5 °C, 18 h, 45%; (b) CAN, CH\(_3\)CN–H\(_2\)O (1:1), 0 °C, 1.5 h, 76%; (c) cyclopentadiene, MeOH, 0 °C, 2 h, 88%; (d) 10% Na\(_2\)CO\(_3\), 50% H\(_2\)O\(_2\), 0 °C, 2 h, 85%; (e) DBU, 35% formalin, THF, 0 °C, 2 h, 86%; (f) diphenyl ether, 240 °C, 6 min, 74%; (g) Ac\(_2\)O, pyridine, DMAP, DCM, 0 °C, 90%.

Scheme 2. Reagents and conditions: (a) DIBAL-H (2.0 equiv), THF, −78 °C, 30 min, 62%; (b) diphenylether, 240 °C, 12 min, 69%; (c) Ac\(_2\)O, pyridine, DCM, −20 °C, 80% based on the recovery of S.M.
found to be in the range of 1.3–1.6 Hz, indicating a trans-relationship of these protons and fully secured the stereochemistry of the yanuthones.

In summary, we have accomplished the first total synthesis of the marine natural products yanuthones A–C and 22-deacetylyanuthone A from commercially available p-methoxyphenol through the intermediacy of 2-farnesyl-p-benzoquinone involving a short, general and stereocontrolled sequence. The strategy outlined here is amenable to adaptation for the synthesis of other members of the farnesylated epoxycyclohexenoid family.

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References and notes

9. All new compounds were characterized on the basis of IR, 1H and 13C NMR and HRMS data. Spectral data for selected compounds: compound 12: 1H NMR (300 MHz, CDCl3) δ 6.78–6.68 (m, 2H), 6.56–6.52 (m, 1H), 5.18–5.07 (m, 3H), 3.14 (d, 2H, δ = 7.5 Hz), 2.14–1.97 (m, 8H), 1.68 (s, 3H), 1.64 (s, 3H), 1.60 (s, 6H), 13C NMR (75 MHz, CDCl3) δ 187.9, 187.6, 148.5, 140.2, 136.7, 136.7, 135.3, 132.3, 131.3, 124.3, 123.7, 117.6, 39.6, 27.4, 26.7, 26.5, 17.7, 17.2, 16.2, 16.1. Compound 18: 1H NMR (400 MHz, CDCl3) δ 6.07 (s, 1H), 6.05 (s, 1H), 5.09–5.05 (m, 2H), 4.92 (t, 1H, δ = 5.4 Hz), 4.38 (d, 1H, δ = 11.6 Hz), 3.81 (d, 1H, δ = 11.2 Hz), 3.42 (s, 1H), 3.31 (br s, 2H), 2.87 (d, 1H, δ = 3.2 Hz), 2.64–2.62 (m, 2H), 2.07–1.95 (m, 8H), 1.69 (s, 1H), 1.60 (s, 9H), 1.53 (d, 1H, δ = 9.6 Hz), 1.46 (d, 1H, δ = 9.6 Hz); 13C NMR (100 MHz, CDCl3) δ 205.8, 204.7, 140.9, 138.1, 138.0, 135.4, 131.5, 124.3, 123.7, 114.8, 68.2, 67.8, 61.8, 53.9, 45.9, 44.3, 43.4, 39.7, 26.7, 26.4, 25.8, 25.6, 17.7, 16.4, 16.1; HRMS (ES) m/z calcd for C24H32O5Na [M+Na]+: 447.2511, found: 447.2526. Compound 2: 1H NMR (300 MHz, CDCl3) δ 6.53 (t, 1H, δ = 1.8 Hz), 5.09–4.96 (m, 3H), 4.96 (dd, 1H, δ = 1.8, 16.8 Hz), 4.81 (dd, 1H, δ = 1.8, 16.8 Hz), 3.67 (s, 1H), 2.89 (dd, 1H, δ = 14.7 Hz), 2.63 (dd, 1H, δ = 6.9, 14.7 Hz), 2.14 (d, 3H, δ = 2.07–1.97 (m, 8H), 1.68 (s, 3H), 1.64 (s, 3H), 1.59 (s, 6H), 13C NMR (75 MHz, CDCl3) δ 192.1, 192.0, 169.8, 143.1, 141.2, 135.5, 132.3, 131.3, 124.3, 123.7, 114.7, 62.4, 59.4, 57.5, 39.7, 26.7, 26.3, 25.7, 25.2, 20.6, 17.7, 16.4, 16.0; HRMS (ES) m/z calcd for C22H19O3Na [M+Na]+: 423.2147, found: 423.2158. Compound 8: 1H NMR (500 MHz, CDCl3) δ 5.96 (s, 1H), 5.18–5.05 (m, 2H), 5.00 (t, 1H, δ = 7.3 Hz), 4.68 (d, 1H, δ = 8.4 Hz), 4.45 (d, 1H, δ = 15.0 Hz), 4.39 (d, 1H, δ = 15.0 Hz), 3.72 (d, 1H, δ = 2.8 Hz), 2.81 (dd, 1H, δ = 8.0, 15.5 Hz), 2.72 (d, 1H, δ = 8.5 Hz), 2.51 (dd, 1H, δ = 7.0, 15.5 Hz), 2.27 (br s, 1H), 2.07–1.95 (m, 8H), 1.68 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H), 13C NMR (100 MHz, CDCl3) δ 193.7, 156.7, 140.1, 135.3, 131.5, 124.3, 123.8, 120.9, 115.9, 66.0, 62.9, 61.4, 59.0, 39.8, 26.7, 26.4, 25.9, 25.8, 17.8, 16.4, 16.1; HRMS (ES) m/z calcd for C22H19O3Na [M+Na]+: 383.2198, found: 383.2206. Compound I: 1H NMR (500 MHz, CDCl3) δ 5.93 (d, 1H, δ = 1.3 Hz), 5.11–5.06 (m, 2H), 5.01 (t, 1H, δ = 7.4 Hz), 4.87 (d, 1H, δ = 15.7 Hz), 4.78 (d, 1H, δ = 15.7 Hz), 4.61 (s, 1H), 3.72 (d, 1H, δ = 3.0 Hz), 2.80 (dd, 1H, δ = 8.0, 15.5 Hz), 2.52 (dd, 1H, δ = 6.8, 15.6 Hz), 2.13 (s, 1H), 2.09–1.95 (m, 8H), 1.68 (s, 3H), 1.60 (s, 9H).
3H), 1.64 (s, 3H), 1.60 (s, 3H), 1.59 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 193.2, 170.5, 151.8, 140.2, 135.3, 131.5, 124.3, 123.8, 122.4, 115.7, 65.5, 62.9, 61.4, 58.9, 39.8, 26.7, 26.4, 25.7, 25.9, 20.8, 17.8, 16.4, 16.1; HRMS (ES) m/z calcd for C\(_{24}\)H\(_{34}\)O\(_5\)Na [M+Na]+: 425.2304, found: 425.2288. Compound 3: \(^1\)H NMR (500 MHz, CDCl\(_3\)) δ 6.14 (d, 1H, J = 1.6 Hz), 5.91 (d, 1H, J = 1.0 Hz), 5.35 (d, 1H, J = 5.0 Hz), 5.13–5.07 (m, 2H), 5.01 (t, 1H, J = 6.8 Hz), 4.27 (d, 1H, J = 16.0 Hz), 4.22 (d, 1H, J = 16.0 Hz), 3.71 (d, 1H, J = 2.8 Hz), 2.83 (dd, 1H, J = 8.0, 15.5 Hz), 2.51 (dd, 1H, J = 7.2, 15.5 Hz), 1.68 (s, 3H), 1.64 (s, 3H), 1.59 (s, 3H), 1.57 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) δ 193.4, 170.2, 152.4, 140.0, 134.9, 129.7, 124.3, 124.0, 123.5, 115.4, 66.8, 61.6, 60.2, 55.7, 39.4, 26.9, 26.5, 25.5, 25.4, 20.5, 17.4, 16.1, 15.7; HRMS (ES) m/z calcd for C\(_{24}\)H\(_{34}\)O\(_5\)Na [M+Na]+: 425.2304, found: 425.2314.


12. The stereo- and regiochemical outcome in the DIBAL-H reduction of 18 can be rationalized in terms of the initial coordination of aluminium with the hydroxyl group and the carbonyl group as shown below. This effectively blocks the preferred \textit{exo}-face, precludes additional coordination of the epoxy oxygen with DIBAL-H and activates the carbonyl group for regioselective reduction. Consequently, reduction takes place from the hindered \textit{endo}-face (see arrows) of the tricyclic system to deliver the observed product 20.

13. In the case of the more flexible epoxycyclohexenone 19, the regio- and stereochemical course of the DIBAL-H reduction is directed by coordination with the epoxy oxygen and intramolecular hydride delivery from the same face, as shown below, to result in the observed stereochemistry of 21.