Total Synthesis and Stereochemical Assignment of (–)-Zenkequinone B

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Received: 01.09.2012; Accepted after revision: 08.10.2012

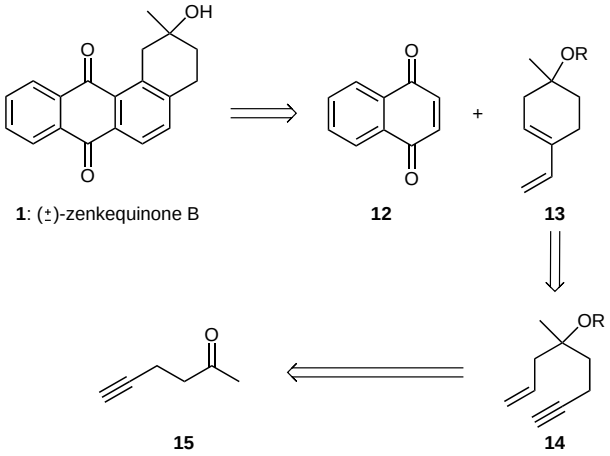
Abstract: The first enantioselective total synthesis and a concise racemic synthesis of zenkequinone B are reported here by utilizing a sequential enyne metathesis, Diels–Alder and aromatization reactions.

Key words: Sharpless epoxidation, enyne metathesis, Diels–Alder reaction, total synthesis

Angucyclinone[1,2] antibiotics, characterized by a benz[*a*]anthraquinone skeleton, display a wide range of biological activities such as antitumor, antifungal, antiviral properties, platelet aggregation, and enzyme inhibitory behavior.[3] To date, more than 200 angucyclinones have been isolated, mainly from *Streptomyces* sp., and they continue to attract synthetic chemists' attention due to their broad biological profile and intriguing structural features. Several strategies have been developed by various research groups to construct the tetracyclic skeleton of angucyclinone. Among them the Diels–Alder reaction has been most widely used method for the successful syntheses of a range of angucyclinones.[4–9] Zenkequinone B, a member of this family, was isolated recently from the stem bark of *Stereospermum zenkeri* by Lenta et al.[10] in 2007 and successfully used as a folk medicine to cure fever and microbial infections. After evaluation of six multiresistant strains of pathogens, it was shown to exhibit the best antimicrobial activity (MIC 9.50 mg/mL) against Gram-negative *Pseudomonas aeruginosa*.[10]

The first and only racemic total synthesis of (±)-zenkequinone B has been reported[11] recently by Yung-Son et al. in five steps from the readily available 2-(chloromethyl)-9,10-dimethoxyanthracene utilizing $TiCl_4$-promoted intramolecular cyclization to get the tetracyclic framework. In continuation of our longstanding interest in the synthesis of angucyclinone natural products[12] and also in exploiting the synthetic utility of sequential enyne metathesis and Diels–Alder reaction,[13] we developed interest in the synthesis of zenkequinone B. We had earlier reported[12b,c] an enantioselective approach to the syntheses of YM-181741, (+)-ochromycinone, (+)-rubiginone B_2, (–)-tetrangomycin, and MM-47755, and recently a unified strategy for the syntheses of tetrangulol, kanglemycin M, X-14881-E, and anhydrolandomycinone (Figure 1).[12a] Herein we report a concise total synthesis of (±)-zenkequinone B and the first enantioselective synthesis of (–)-zenkequinone B, thereby assigning the absolute configuration of the natural product.

Our strategy for the synthesis of racemic zenkequinone B (**1**) is shown in Scheme 1. We envisioned that the angular benz[*a*]anthraquinone skeleton of zenkequinone B (**1**) could be synthesized from diene **13** and dienophile **12** through a Diels–Alder reaction and aromatization. Based on our earlier experience,[12,13] we envisioned that diene **13** could be easily prepared from enyne **14** via an intramolecular enyne metathesis, and the enyne **14** could be traced back to the ketone **15** in a couple of steps. The proposed strategy appears to be rapid and attractive compared to the existing synthesis.

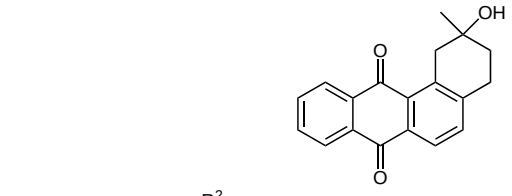


Scheme 1 General retrosynthetic analysis

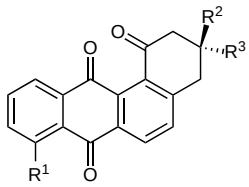
As shown in Scheme 2, our synthesis of (±)-zenkequinone B (**1**) commenced with the addition of allylmagnesium bromide to ketone **15** to furnish enyne **16**[14] which was then refluxed with Grubbs' first-generation catalyst (**17**)[15] to generate the diene **18** in 80% yield. Having synthesized diene in good quantity, the final and key one-pot Diels–Alder reaction of diene **18** with 1,4-naphthoquinone **12** followed by aerobic oxidative aromatization with silica gel and Et_3N was attempted. Pleasingly, this one-pot reaction proceeded cleanly to afford (±)-zenkequinone B (**1**) in 85% yield. The spectroscopic data of the synthetic material were in good agreement with the natural product in all aspects, and thus, we have accomplished the shortest total synthesis of (±)-zenkequinone B (**1**)[10,11] in 68% overall yield from the known enyne **16**[14] (Scheme 2).

After completing the racemic synthesis of zenkequinone B, we then looked at the possibility of accomplishing an enantioselective total synthesis of zenkequinone B, as it is

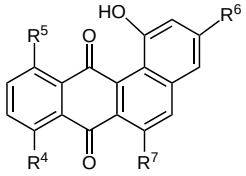
SYNLETT 2012, 23, 2931–2934
Advanced online publication: 09.11.2012
DOI: 10.1055/s-0032-1317519; Art ID: ST-2012-D0732-L



1: (±)-zenkequinone B

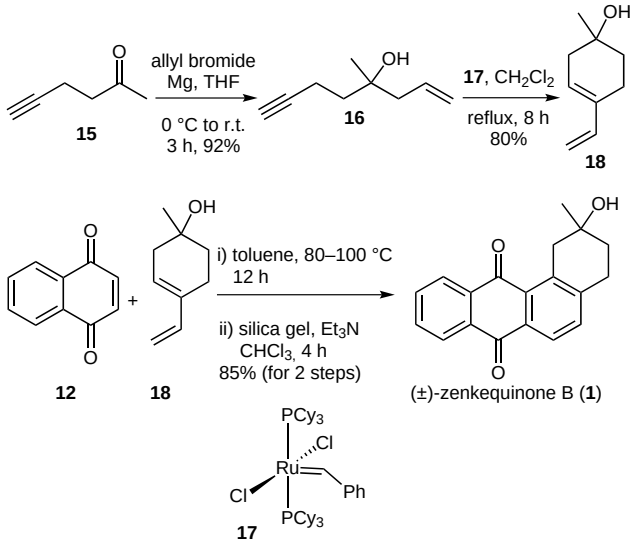


2: R^1 = OH, R^2 = Me, R^3 = H
(+)-ochromycinone
3: R^1 = OMe, R^2 = Me, R^3 = H
(+)-rubiginone B_2
4: R^1 = OH, R^2 = CH_2OH, R^3 = H
YM-181741
5: R^1 = OH, R^2 = Me, R^3 = OH
(–)-tetrangomycin
6: R^1 = OMe, R^2 = Me, R^3 = OH
MM-47755



7: R^4 = OH, R^5 = H, R^6 = Me, R^7 = H
tetrangulol
8: R^4 = OH, R^5 = H, R^6 = CH_2OH, R^7 = H
kanglemycin M
9: R^4 = OMe, R^5 = H, R^6 = Me, R^7 = H
X-14881-E
10: R^4 = OH, R^5 = OH, R^6 = Me, R^7 = H
anhydrolandomycinone
11: R^4 = OH, R^5 = H, R^6 = Me, R^7 = OH
dehydrorabelomycin

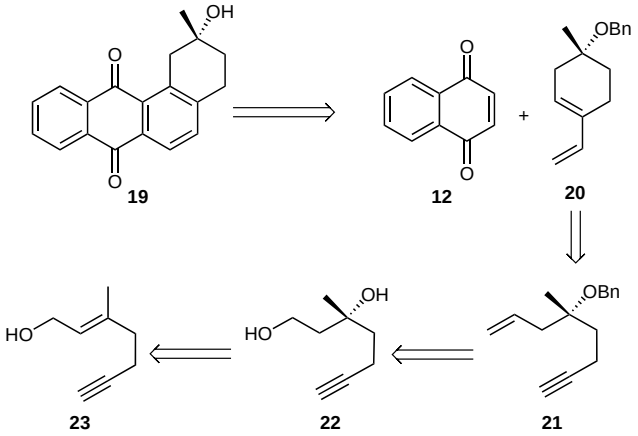
Figure 1 Angucyclinone antibiotics of our interest



Scheme 2 Racemic synthesis of (±)-zenkequinone B

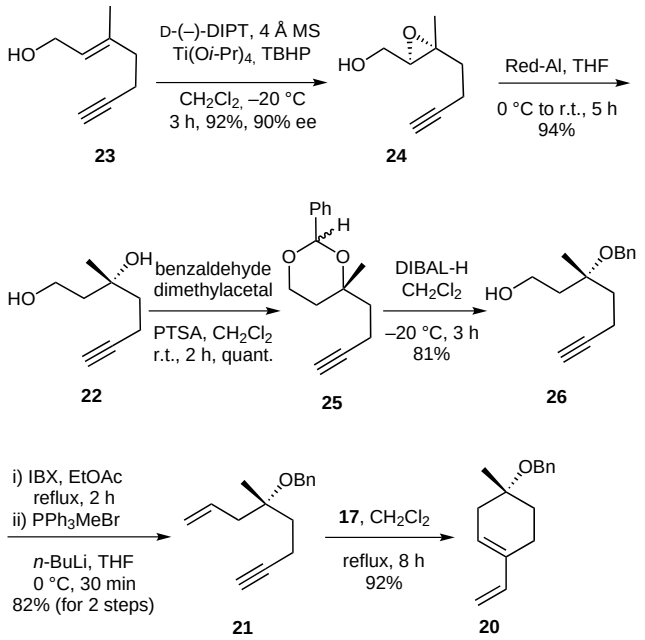
important to elucidate its absolute configuration which had not been determined. With this objective, we designed a simple and efficient strategy for the asymmetric synthesis of zenkequinone B as shown in Scheme 3. To this end, our first goal was to synthesize the diene **20**[19] in enantiomerically enriched form, which obviously could be generated from the enyne **21** via enyne metathesis. Of further interest was to utilize Sharpless asymmetric epoxidation[16] followed by a reductive opening of the resulting epoxide to introduce the lone quaternary chiral center. Thus, we envisaged that the known allylic alcohol **23**[17] would serve as the appropriate starting material for the proposed asymmetric synthesis of zenkequinone B.

As delineated in Scheme 4, our synthetic strategy for the asymmetric synthesis of zenkequinone B began with the Sharpless asymmetric epoxidation[16] of allylic alcohol **23** to provide epoxy alcohol **24** in 92% yield and 90% enantionmeric excess (Mosher ester analysis).



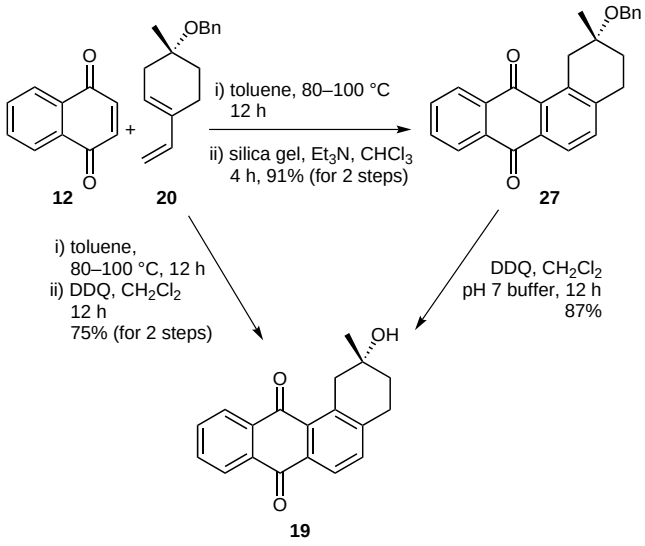
Scheme 3 Retrosynthetic analysis for (–)-zenekequinone B

Reductive opening of the epoxide was then successfully accomplished using Red-Al to furnish the 1,3-diol **22** in 94% yield. The diol was subsequently protected as a benzylidene derivative by treatment with benzaldehyde dimethylacetal in the presence of PTSA to provide **25** in quantitative yield. A regioselective opening of the benzylidene derivative **25** with DIBAL-H delivered the primary alcohol **26** with concomitant protection of the tertiary alcohol as benzyl ether in 81% yield. Oxidation of alcohol **26** with IBX and subsequent Wittig reaction of the resulted crude aldehyde afforded enyne **21** in 82% yield.



Scheme 4 Enantioselective synthesis of diene

Having the enyne **21** in hand, the key ring-closing enyne metathesis and Diels–Alder reaction were left to complete the synthesis of zenkequinone B. As expected, the ring-closing enyne metathesis worked very well with Grubbs' first-generation catalyst **17** to afford diene **20** in excellent yield (Scheme 4).



Scheme 5 Enantioselective total synthesis of (–)-zenkequinone B

After having the required diene in good quantity as well as in high enantiomeric excess we investigated the Diels–Alder reaction. In this regard, treatment of diene **20** with 1,4-naphthoquinone **12** followed by silica gel/Et_3N-mediated oxidative aromatization provided the tetracyclic compound **27**[20] in 91% yield. Unfortunately, all our efforts to cleave the benzyl group using a Lewis acid following our earlier report[12a] were unsuccessful under various conditions. After extensive experimentation, the benzyl group was eventually cleaved using DDQ to furnish (–)-zenkequinone B in 87% yield. The structure of **19**[21] was confirmed by NMR, mass, IR analyses, and all recorded data were in good accordance with the published data. The enantiomeric excess of (–)-zenkequinone B (**19**) was determined to be ≥84% according to chiral HPLC [t_R of (–)-**19**/(+)-**19** = 33.15:38.05][18]. Furthermore, the specific rotation of our synthetic zenkequinone B {**19**; $[\alpha]_D^{25}$ –195.33 (*c* 0.06, acetone)} was comparable with that of reported[9b] value {$[\alpha]_D^{25}$ –236 (*c* 0.05, acetone), Scheme 5}. In addition, CD spectra (see the Supporting Information) of **19** displayed a negative Cotton effect near λ = 344 nm. Hence, the asymmetric synthesis of **1** from enantioenriched epoxyalcohol **24** proves the 2*R* absolute configuration of (–)-zenkequinone B unequivocally.

In summary, we have successfully accomplished a short and efficient total synthesis of (±)-zenkequinone B in 68% overall yield (three steps). We also have achieved the first enantioselective synthesis of (–)-zenkequinone B in 42% overall yield (eight steps) by employing an intramolecular enyne metathesis, Diels–Alder reaction, and aromatization as key steps.

Acknowledgment

We thank DST, New Delhi for financial support. K.P.K. thanks DST for the award of Swarnajayanti fellowship. D.G.V. thanks UGC, New Delhi for a fellowship.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(18) HPLC separation conditions: The ee value was determined by CHIRALCEL OD-H, *n*-hexane–2-PrOH = 90:10, flow rate: 0.5 mL/min, λ = 256 nm.
(19) **(*R*)-[(1-Methyl-4-vinylcyclohex-3-enyloxy)methyl]benzene (20)**
A solution of enyne **21** (500 mg, 2.19 mmol) in CH_2Cl_2 (60 mL) was treated with Grubbs' first-generation catalyst (**17**; 133 mg, 7 mol%) and then refluxed for 8 h. The reaction mixture was cooled to r.t. and stirred with DMSO (50 equiv with respect to the catalyst) for 6 h to remove the metal impurities. Evaporation of the solvent and purification by silica gel flash column chromatography (10% EtOAc in hexanes) provided 1,3-diene **20** (460 mg, 92%); R_f = 0.7 (EtOAc–hexanes, 1:9); $[\alpha]_D^{21}$ +67.6 (*c* 3.6, $CHCl_3$). IR (neat): 2929, 2846, 1645, 1614, 1513, 1462, 1378, 1247, 1129, 1098, 1036, 821, 758 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.28 (m, 4 H), 7.26–7.20 (m, 1 H), 6.37 (dd, *J* = 17.5, 10.7, Hz, 1 H), 5.64 (s, 1 H), 5.08 (d, *J* = 17.5 Hz, 1 H), 4.93 (d, *J* = 10.7 Hz, 1 H), 4.51, 4.44 (ABq, *J* = 18.0 Hz, 2 H), 2.45 (d, *J* = 18.2 Hz, 1 H), 2.40–2.32 (m, 1 H), 2.20 (d, *J* = 18.2 Hz, 1 H), 2.17–2.12 (m, 1 H), 1.97–1.90 (m, 1 H), 1.78–1.71 (m, 1 H), 1.30 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.9, 139.5, 135.4, 128.4, 127.4, 127.2, 127.0, 110.6, 73.6, 63.6, 37.6, 32.6, 23.6, 22.1. ESI-HRMS: *m/z* calcd for $C_{16}H_{20}O$ $[M + Na]^+$: 251.1412; found: 251.1404.
(20) **(*R*)-2-(Benzyloxy)-2-methyl-1,2,3,4-tetrahydrotetraphene-7,12-dione (27)**
A solution of naphthoquinone **12** (228 mg, 1.44 mmol) and diene **20** (300 mg, 1.31 mmol) in toluene was heated at 80 °C for 12 h and then at 100 °C for 2 h. After the solvent was removed in vacuo, the crude Diels–Alder adduct was dissolved in $CHCl_3$ (2 mL), treated with Et_3N (1 mL) and silica gel (1 g) and stirred for 4 h. The solvent was removed in vacuo and purified by a silica gel flash column chromatography (20% EtOAc in hexanes) to afford the tetracycle **27** (460 mg, 91%) as a pale yellow solid; R_f = 0.6 (EtOAc–hexanes, 1:3); mp 163–165 °C; $[\alpha]_D^{21}$ –233.55 (*c* 1.1, $CHCl_3$). IR (neat): 3021, 2961, 2926, 2857, 1663, 1581, 1566, 1454, 1326, 1299, 1270, 1099, 1045, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.24–8.19 (m, 2 H), 8.16 (d, *J* = 8.0 Hz, 1 H), 7.79–7.71 (m, 2 H), 7.52 (d, *J* = 8.0 Hz, 1 H), 7.15–7.05 (m, 5 H), 4.53, 4.43 (ABq, *J* = 11.7 Hz, 2 H), 3.85 (d, *J* = 19.0 Hz, 1 H), 3.26–3.20 (m, 1 H), 3.22 (d, *J* = 19.0 Hz, 1 H), 2.92–2.85 (m, 1 H), 2.22–2.17 (m, 1 H), 1.87–1.79 (m, 1 H), 1.56 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 185.9, 183.7, 145.0, 139.6, 138.7, 135.2, 134.3, 134.1, 133.4, 133.3, 132.7, 131.7, 128.2, 127.2, 127.1, 126.5, 125.2, 72.9, 63.8, 39.9, 32.1, 27.6, 25.4. ESI-HRMS: *m/z* calcd for $C_{26}H_{22}O_3$ $[M + Na]^+$: 405.1467; found: 405.1475.
(21) **(–)-Zenkequinone B (19)**
A solution of benzyl ether **27** (50 mg, 0.13 mmol) in a mixture of CH_2Cl_2 (10 mL) and pH 7 buffer (0.5 mL) at 0 °C was treated with DDQ (59 mg, 0.26 mmol) portionwise and allowed to stir at r.t. for 12 h. The reaction mixture was treated with a sat. solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4), concentrated, and purified by silica gel column chromatography to afford target compound **19** (33 mg, 87%) as a pale yellow solid; R_f = 0.40 (EtOAc–hexanes, 1:2); mp 202–204 °C; $[\alpha]_D^{21}$ –195.33 (*c* 0.06, acetone). IR (neat): 3463, 3082, 2961, 2927, 1663, 1579, 1561, 1368, 1329, 1303, 1275, 1092, 1045, 759 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.21–8.15 (m, 2 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 7.76–7.70 (m, 2 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 3.57 (d, *J* = 18.8 Hz, 1 H), 3.35 (d, *J* = 18.8 Hz, 1 H), 3.27–3.18 (m, 1 H), 2.91 (dt, *J* = 16.4, 4.4 Hz, 1 H), 1.98–1.92 (m, 1 H), 1.85–1.77 (m, 1 H), 1.47 (s, 3 H). ESI-HRMS: *m/z* calcd for $C_{19}H_{16}O_3$ $[M + Na]^+$ 315.0997; found: 315.0994.

