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Total synthesis of tovophyllin B

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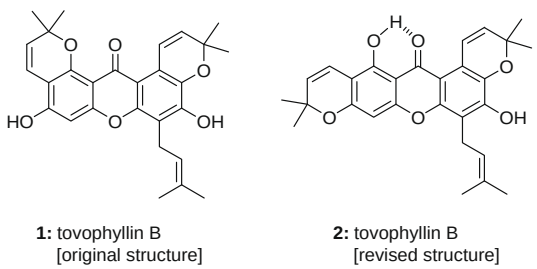
ABSTRACT

The first total synthesis of tovophyllin B (**2**), an antimicrobial xanthone derived from mangosteen, has been accomplished through a convergent strategy from building blocks **6** and **7** involving lithium-mediated coupling, dehydrative cyclization, and 6π electrocyclization as key steps.

Tovophyllin B, a prenylated pentacyclic xanthone, was first isolated in 1972 from the wood of *Tovomita macrophylla* by de Oliveira et al.[1] The originally proposed structure (**1**; Fig. 1) was corrected in 1975 on the basis of chemical and spectroscopic data to the currently accepted structure (**2**, Fig. 1) in which one of the phenolic groups is H-bonded to the carbonyl moiety of the molecule.[2] Recent investigations of the antituberculosis potential of the fruit hulls of mangosteen (*Garcinia mangostana*), traditionally used in Thai folk medicine for alleviation of a number of maladies, led to re-isolation of this natural product, and revealed that tovophyllin B (**2**) possesses a significant inhibitory activity against *Mycobacterium tuberculosis* (MIC = 25 μg/mL).[3] Therefore, as a lead compound for drug discovery, the total synthesis of tovophyllin B and its analogs is deemed important. In this Letter, we report a short and efficient total synthesis of this molecule that may also serve to prepare designed analogs.

Scheme 1 shows the retrosynthetic analysis of the molecule of tovophyllin B (**2**) in which a 6π electrocyclization (a) plays the role of casting the final heterocyclic ring in the synthetic direction (**3**→**2**). An aldol/dehydration sequence (b) then traces **3**, expected to be a transient intermediate, back to xanthone **4** and prenal (**4′**). Disconnection of the indicated carbon–oxygen bond within xanthone **4** through a retro dehydrative cyclization leads to bisaryl ketone **5**, whose disassembly through a retro lithium-mediated coupling as shown reveals benzaldehyde **6** and benzopyran derivative **7** as the required building blocks for the projected synthesis.

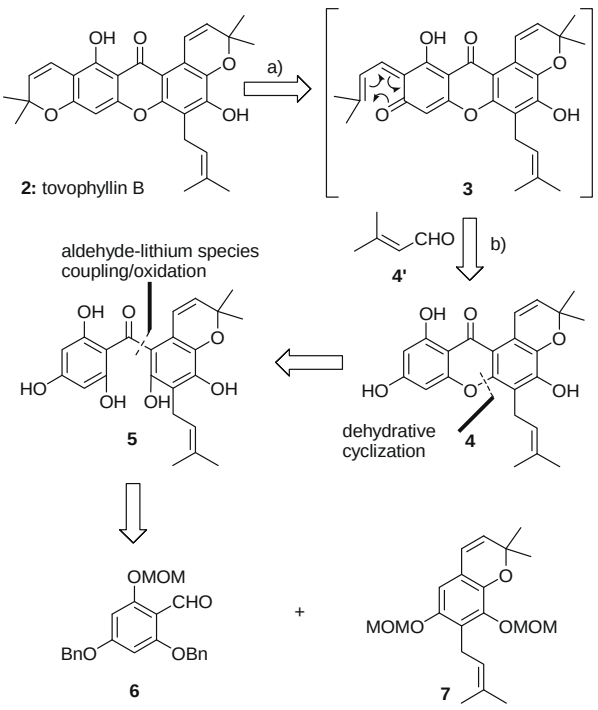
Scheme 2 summarizes the synthesis of advanced intermediate bisaryl ketone **5**. Thus, O-propargylation[4] of the readily available phenol **8** (prepared from 2,4-dihydroxybenzaldehyde in three steps)[5] with methyl 2-methyl-3-yn-2-yl carbonate (**9**) in the



1: tovophyllin B
[original structure]

2: tovophyllin B
[revised structure]

Figure 1. Originally proposed (**1**) and revised (**2**) structures of tovophyllin B.



Scheme 1. Retrosynthetic analysis of tovophyllin B (**2**): (a) 6π electrocyclization; (b) aldol/dehydration.

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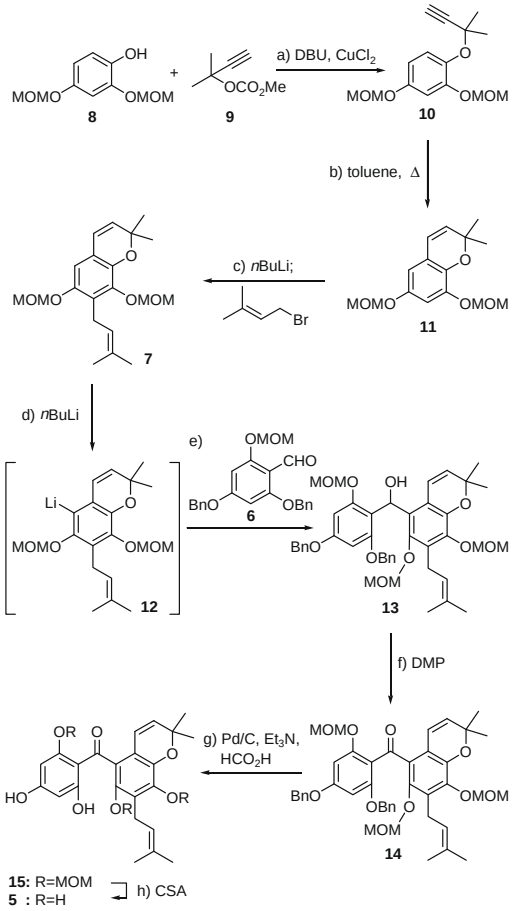
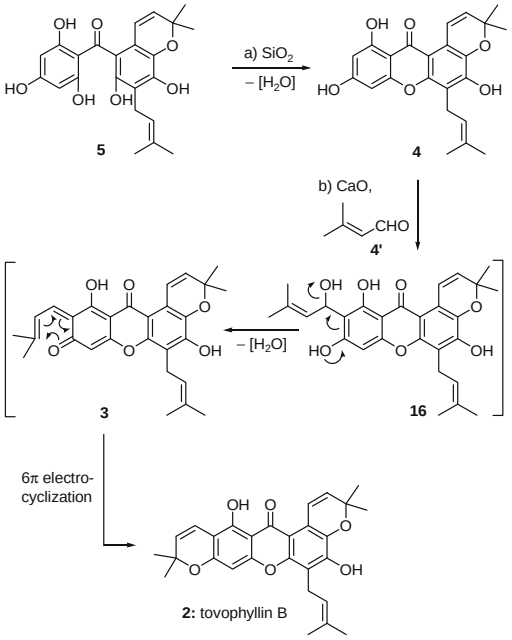


Scheme 2. Synthesis of bisaryl ketone **5**. Reagents and conditions: (a) **9** (3.0 equiv), DBU (3.0 equiv), $CuCl_2$ (0.01 equiv), MeCN, 0 °C, 12 h; (b) toluene, 140 °C, 48 h, 74% (over two steps); (c) *n*BuLi (1.3 equiv), THF, 25 °C, 15 min; then prenyl bromide (1.5 equiv), THF, 25 °C, 2 h, 86%; (d) *n*BuLi (1.5 equiv), THF, 25 °C, 15 min; (e) **6** (1.5 equiv), THF, −78 °C, 15 h, 58%; (f) DMP (1.4 equiv), $NaHCO_3$ (5.0 equiv), CH_2Cl_2, 25 °C, 2 h, 80%; (g) 10% Pd/C (0.34 equiv), Et_3N (1.0 equiv), HCO_2H (32 equiv), acetone, 25 °C, 1.5 h, 89%; (h) CSA (5.0 equiv), MeOH, 25 °C, 8 h.

presence of DBU and catalytic amounts of $CuCl_2$ proceeded smoothly to afford 1,1-dimethylpropargyl ether **10**, which, upon heating in toluene at 140 °C, underwent Claisen rearrangement, leading to 2,2-dimethylchromene **11**, in 74% overall yield for the two steps.[6]

Regioselective lithiation of **11** facilitated by the two OMOM groups (*n*BuLi, THF, 25 °C), followed by quenching of the resulting lithiated species with prenyl bromide furnished prenylated chromene **7** in 86% yield. Pleasantly, the generation of the lithiated species **12** from **7** proceeded smoothly on exposure of the latter to *n*BuLi in THF at 25 °C and was essentially complete within 15 min (ca. 95% deuterium incorporation upon quenching with D_2O). Addition of bis-benzyl-MOM-protected benzaldehyde derivative **6** (prepared from phloroglucinol carboxaldehyde in two steps)[7] to lithiated species **12** at −78 °C furnished coupling product **13** (58% yield),[8] whose hydroxy group was oxidized with Dess–Martin periodinane to afford ketone **14**,[9] in 80% yield. Initial attempts to selectively remove the benzyl groups from the latter compound with hydrogen and a variety of catalysts failed primarily due to the interference of the olefinic bonds residing within the molecule. This problem was, however, solved through the employment of a palladium-catalyzed transfer hydrogenation protocol utilizing a triethylammonium formate/formic acid buffer system.[10] Under these conditions, the two benzyl groups were cleanly cleaved from **14** to form the corresponding diphenol (**15**, 89% yield), from which the MOM groups were removed by exposure to CSA in MeOH at ambient temperature, leading to the desired tricyclic precursor **5**.



Scheme 3. Completion of the total synthesis of tovophyllin B (**2**). Reagents and conditions: (a) impregnation on a silica gel plate (1.5 h); then elution with EtOAc, 65% (for two steps), (b) CaO (7.5 equiv), prenal (**4′**) (15 equiv), MeOH, 25 °C, 16 h, 55%.

The final steps of the synthesis of tovophyllin B (**2**) are shown in Scheme 3. Thus, cycloetherification of **5** under the influence of silica gel (impregnation of the substrate on a silica gel plate, followed by elution with EtOAc)[11] furnished, through dehydration, xanthone **4**[9] in 65% yield (for two steps). The missing 2,2-dimethylchromene ring of the growing molecule was finally forged through a cascade sequence involving CaO-induced aldol-type reaction[12] of xanthone **4** with prenal (**4′**) that proceeded via intermediates **16** and **3** to afford the target molecule (**2**) in 55% overall yield as shown in Scheme 3. Synthetic tovophyllin B (**2**) exhibited identical physical properties to those reported for the naturally derived material.[1,2]

The described chemistry demonstrates the power of cascade reactions in total synthesis,[13] and provides a practical route to tovophyllin B (**2**) and related compounds, including designed analogs for biological investigations.

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9. Physical properties of selected compounds. **14**: IR (film): ν_{max} 3065, 2974, 2928, 1650, 1600, 1582, 1430, 1322, 1206, 1152, 1112, 1067, 926, 843, 731, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.18 (m, 10H), 6.43 (d, J = 9.9 Hz, 1H), 6.42 (s, 1H), 6.28 (d, J = 1.8 Hz, 1H), 5.53 (d, J = 9.9 Hz, 1H), 5.18 (t, J = 6.6 Hz, 1H), 5.12 (s, 2H), 5.04 (s, 2H), 4.96 (s, 2H), 4.94 (s, 2H), 4.69 (s, 2H), 3.56 (s, 3H), 3.41 (d, J = 6.3 Hz, 2H), 3.31 (s, 3H), 3.29 (s, 3H), 1.71 (s, 3H), 1.63 (s, 3H), 1.41 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.99, 162.03, 159.07, 158.08, 146.98, 144.88, 141.80, 136.12, 136.09, 131.03, 130.36, 129.98, 129.45, 128.54, 128.34, 128.14, 127.61, 127.58, 126.84, 120.30, 119.09, 115.39, 101.27, 98.59, 94.72, 94.63, 94.28, 75.41, 70.39, 70.06, 57.37, 57.23, 55.99, 27.50, 25.58, 24.01, 17.89; HRMS(ESI-TOF) m/z calcd for $C_{43}H_{49}O_{10}$ ($M+H^+$) 725.3320, found 725.3320. Compound **4**: IR (film): ν_{max} 3356, 2973, 2925, 2876, 1650, 1612, 1570, 1431, 1321, 1293, 1253, 1167, 1138, 1084, 1031, 966, 893, 830, 813, 768 cm^{-1}; ^1H NMR (400 MHz, MeOH-d_4) δ 7.92 (d, J = 10 Hz, 6.22 (s, 1H), 6.09 (s, 1H), 5.76 (d, J = 10 Hz, 1H), 5.23 (t, J = 7.6 Hz, 1H), 3.51 (d, J = 7.2 Hz, 2H), 1.87 (s, 3H), 1.67 (s, 3H), 1.45 (s, 6H); ^{13}C NMR (100 MHz, MeOH-d_4) δ 182.54, 164.73, 163.37, 163.36, 157.33, 151.05, 150.22, 137.61, 131.59, 131.40, 131.38, 121.53, 120.84, 117.50, 177.49, 115.60, 107.35, 102.77, 97.49, 92.82, 75.75, 26.05, 24.74, 22.21, 16.96; HRMS (ESI-TOF) m/z calcd for $C_{23}H_{23}O_6$ ($M+H^+$) 395.1489, found 395.1491.
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