Stereoselective Formal Total Synthesis of (–)-Didemniserinolipid B

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Abstract: A formal total synthesis of (–)-didemniserinolipid B from L-(+)-tartaric acid is presented. Key features of the synthesis include construction of the bicyclic acetal core from bisdimethyl amide of tartaric acid and further elaboration by cross metathesis.

Key words: didemniserinolipid B, marine natural product, stereoselective synthesis, tartaric acid

Alkylated 6,8-dioxabicyclo[3.2.1]octane structural units are widespread in bioactive natural products. Pine beetle pheromones such as brevicomins contain simple 6,8-dioxabicyclo[3.2.1]octane unit while didemniserinolipids that originate from marine sources possess complex systems with the same bicylic core.[1] Didemniserinolipid B (**1**, Figure 1) isolated from the marine tunicate belonging to the genus *Didemnum sp.* by Gonzalez et al.[2] possess the 6,8-dioxabicyclo[3.2.1]octane framework with an extended alkyl chains, containing a 2-aminopropane 1,3-diol ether, and a α,β-unsaturated ester. Although didemniserinolipid B showed no appreciable bioactivity, interesting bioactive profile of related didemniserinolipids as inhibitors of HIV-1 integrase[3] has invigorated the attention of synthetic chemists. Ley's group has synthesized natural didemniserinolipid B and also revised the structure and absolute configuration of the natural product.[4a] Burke's group recently reported the synthesis of didemniserinolipid B employing their ketalization–ring-closing-metathesis strategy,[4b,c] while a formal synthesis of **1** by Ramana and Induvadana involving a Pd-mediated alkynediol cycloisomerization was disclosed.[4d] Our own interest in the synthesis of 6,8-dioxabicyclo[3.2.1]octane-containing natural products and other oxygenated natural products, culminated in enantiodivergent synthesis of hydroxy-*exo*-brevicomin, hydroxy brevicomin from chiral-pool tartaric acid.[5] In continuation of our efforts, herein we report a stereoselective formal total synthesis of the antipode of natural didemniserinolipid B from L-(+)-tartaric acid.

Our approach for the synthesis of (–)-**1** is based on the elaboration of bicyclic acetal **11**. Installation of the C15 side chain is planned by cross metathesis followed by hydrogenation, while formation of the α,β-unsaturated ester is envisaged by Wittig olefination. Synthesis of the bicylic acetal **11** is anticipated by intramolecular ketalization of the masked triol **7**, the synthesis of which from the keto amide **3** derived from tartaric acid[6] is envisioned (Scheme 1).

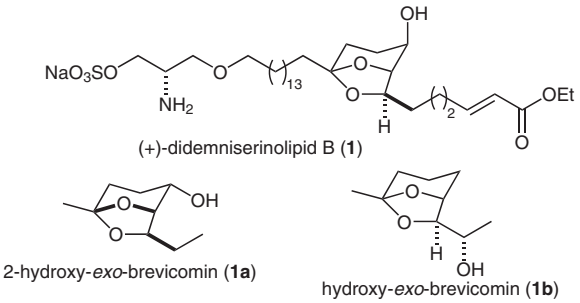
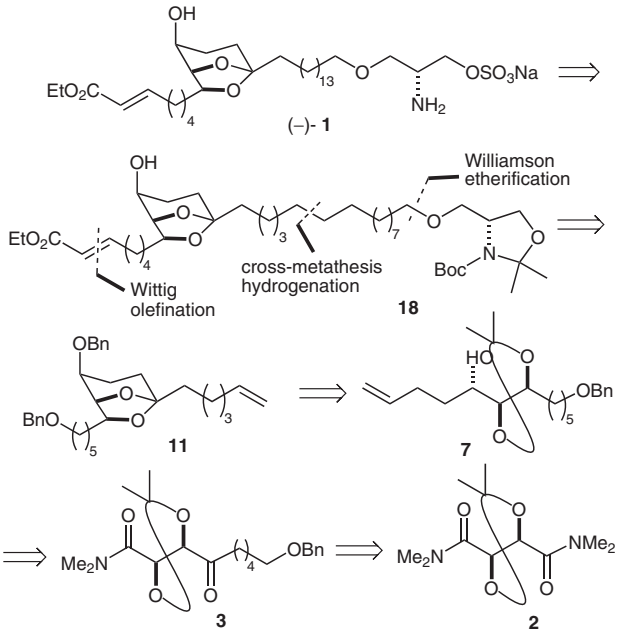


Figure 1 Natural products possessing 6,8-dioxabicyclo[3.2.1]octane framework



Scheme 1 Retrosynthesis for (–)-didemniserinolipid

Accordingly, the synthetic sequence commenced with the addition of 1.5 equivalents of 4-benzyloxy-butylmagnesium bromide to the bisdimethylamide derived from tartaric acid **2** resulting in the ketoamide **3** in 86% yield.[7] Reduction of the ketone in **3** with $NaBH_4/CeCl_3$ furnished the alcohol **4** in 93% yield,[8] which under Barton–McCombie deoxygenation[9] conditions afforded the amide **5** in 72% yield for two steps. Addition of 3-butenylmagnesium bromide to amide **5** produced the corresponding ketone in 86% yield, which on reduction with K-Selectride in THF at –78 °C furnished the alcohol **6** as a single diastereomer

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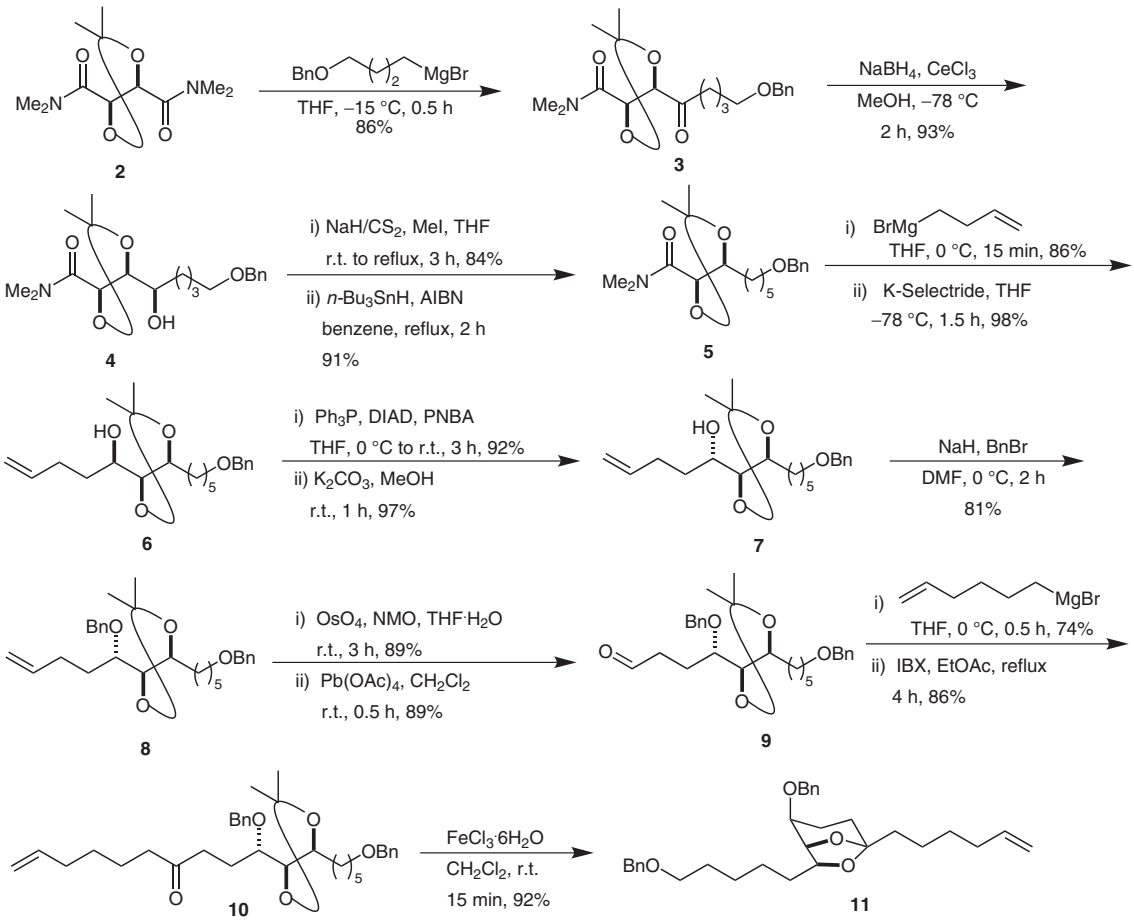

Scheme 2 Synthesis of 6,8-dioxabicyclo[3.2.1]octane fragment of didemniserinolipid B

in 98% yield. Mitsunobu inversion of the secondary hydroxy group in **6** with DIAD, Ph_3P, and *p*-nitrobenzoic acid, and subsequent hydrolysis of the *p*-nitrobenzoyl ester furnished the epimerized alcohol **7** in 94% yield for two steps. The free hydroxy group in **7** was protected as the corresponding benzyl ether **8** using standard conditions in 81% yield. Osmium-mediated dihydroxylation of the alkene furnished the corresponding diol which on treatment with $Pb(OAc)_4$ produced the aldehyde **9** in 89% yield for two steps. Addition of 5-hexenylmagnesium bromide to the aldehyde **9** furnished a diastereomeric mixture of the corresponding alcohol in 74% yield, which was subjected to oxidation with IBX to yield the ketone **10** in 86% yield. Treatment of **10** with $FeCl_3$ smoothly furnished the bicyclic acetal **11** in 92% yield (Scheme 2).[10]

Reaction of the bicyclic acetal **11** with 10-undecenoic acid methyl ester mediated by Grubbs' second-generation catalyst was facile affording the product **12** in 80% yield.[11] Hydrogenation of the alkene in **12** with Pd/C followed by reduction with $LiAlH_4$ produced the alcohol **13**[12] in almost quantitative yield. Alcohol **13** was transformed into the mesylate, which on further reaction with L-serinol derivative **14** afforded **15** in 56% yield for two steps. Debenzylation of the bisbenzylether **15** produced the diol **16** in 95% yield. Subjecting the diol **16** to Dess–Martin periodinane oxidation followed by Wittig olefination with the ylide **17** resulted in the known α,β-unsaturated ester **18** in 59% yield. Conversion of **18** to didemniserinolipid B is reported by Burke et al. The present sequence thus constitutes a formal total synthesis of (–)-didemniserinolipid B (Scheme 3).

In conclusion, a stereoselective formal total synthesis of (–)-didemniserinolipid B from the bisdimethylamide of tartaric acid was presented. Key features of the synthetic sequence include the formation of the 6,8-dioxabicyclo[3.2.1]octane core by intramolecular ketalization of a keto triol derived from tartaric acid and the installation of the alkyl chain on the bicylic acetal via cross metathesis followed by hydrogenation. The synthetic sequence depicted is amenable for the synthesis of a number of analogues.

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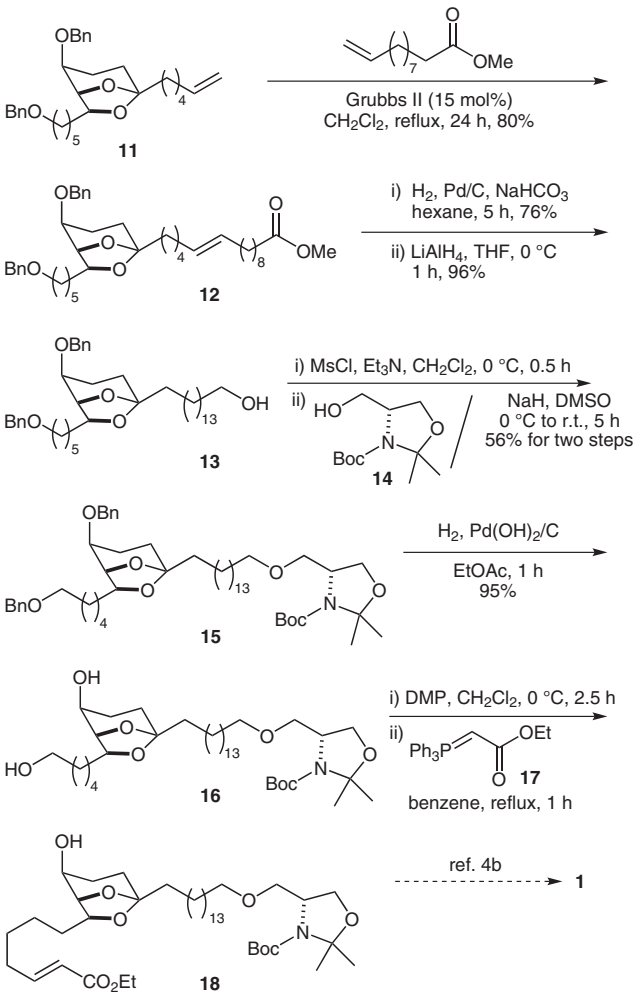

Scheme 3 Formal total synthesis of (–)-didemniserinollipid B

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(7) Formation of minor amount (8%) of diketone resulting from the addition of Grignard reagent to both amide groups is observed.

(8) Diastereomeric ratio of the product alcohol was estimated to be >95:5 within detectable limits by ^{1}H NMR. Alcohols were inseparable at this stage. However, stereochemistry of the alcohol is of no consequence because it is deoxygenated in the next step.

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(11) It was cumbersome to purify the cross-metathesis product **12** by column chromatography from traces of an unidentified impurity. However, this was of no consequence in the next reaction sequence, and pure **13** was isolated after the reduction of the olefin and the ester.

(12) All new compounds exhibited satisfactory spectral data. In the NMR data that follow, * indicates rotamer peaks.
Compound **3**: $[\alpha]_D$ +8.7 (*c* 1.3, $CHCl_3$). IR (neat): 2940, 2863, 1716, 1652, 1506, 1374 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.24 (m, 5 H), 5.13 (d, *J* = 6.0 Hz, 1 H), 4.78 (d, *J* = 5.7 Hz, 1 H), 4.90 (s, 2 H), 3.47 (t, *J* = 6.0 Hz, 2 H), 3.13 (s, 3 H), 2.98 (s, 3 H), 2.83–2.56 (m, 2 H), 1.79–1.55 (m, 4 H), 1.42 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.2, 168.1, 138.5, 128.3, 128.3, 127.6, 127.5, 112.1, 82.1, 74.9, 72.9, 69.9, 39.2, 37.0, 36.0, 29.1, 26.4, 26.0, 19.8. HRMS: *m/z* calcd for $C_{18}H_{25}NO_5$ + Na: 386.1943; found: 386.1925
Compound **13**: $[\alpha]_D$ –21.2 (*c* 3, $CHCl_3$). IR (neat): 3448, 2926, 1455, 1097, 734 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.10 (m, 10 H), 4.62 (s, 2 H), 4.5 (s, 2 H), 4.17 (br s, 1 H), 3.90–3.73 (m, 1 H), 3.63 (t, *J* = 6.6 Hz, 2 H), 3.46 (t, *J* = 6.6 Hz, 2 H), 3.29 (br s, 1 H), 2.30 (t, *J* = 7.5 Hz, 2 H), 2.00–1.15 (m, 40 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.7, 138.5, 128.37, 128.32, 127.63, 127.58, 127.47, 109.3, 80.0, 77.8, 72.8, 72.3, 70.3 (2 C), 63.1, 37.4, 35.3, 32.8, 30.7, 29.8, 29.62, 29.58, 29.41, 26.1, 25.7, 25.4, 22.8, 22.0. HRMS: *m/z* calcd for $C_{40}H_{62}O_5$ + Na: 645.4495; found: 645.4484.
Compound **15**: $[\alpha]_D$ –18.3 (*c* 0.3, $CHCl_3$). IR (neat): 3069, 2927, 1700, 1454, 1388, 734 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.20 (m, 10 H), 4.61 (s, 2 H), 4.49 (s, 2 H), 4.17 (br s, 1 H), 4.10–3.85 (m, 3 H), 3.85–3.70 (m, 1 H), 3.70–3.30 (m, 6 H), 3.29 (br s, 1 H), 2.00–1.15 (m, 55 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.2/151.7*, 138.7/138.5*, 128.4, 128.35, 127.66, 127.60, 127.5, 109.3, 93.7/93.3*, 80.1/79.7*, 80.0, 77.8, 72.9, 72.3, 71.4, 70.3 (2 C), 70.1/69.3*, 65.7/65.4*, 56.5/56.4*, 37.43, 35.3, 30.8, 29.8, 29.7, 29.64, 29.60, 29.5, 28.48, 28.43, 27.5/26.8*, 26.11, 26.06, 25.43, 24.4/23.1*, 22.8, 21.96. HRMS: *m/z* calcd for $C_{51}H_{81}NO_8$ + Na: 858.5860; found: 858.5861.
Compound **16**: $[\alpha]_D$ –41.4 (*c* 1.2, $CHCl_3$) [Lit.[4d] $[\alpha]_D$ +36.3 (*c* 0.2, $CHCl_3$ for the enantiomer)]. IR ($CHCl_3$): 3463, 2928, 1700, 1389, 1366, 1088, 770 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.07 (br s, 1 H), 4.05–3.96 (m, 1 H), 3.95–3.86 (m, 3 H), 3.65 (t, *J* = 6.5 Hz, 2 H), 3.62–3.55 (m, 1 H), 3.54–3.37 (m, 2 H), 3.36–3.14 (m, 2 H), 2.52–2.30 (m, 1 H), 2.10–1.81 (m, 1 H), 1.79–1.41 (m, 30 H), 1.38–1.22 (m, 25 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.2/151.7*, 109.6, 93.7/

93.3*, 82.4, 80.3/79.7*, 77.8, 71.4, 70.0/69.3*, 66.3, 65.7/65.4*, 56.5/56.3*, 37.5, 35.2, 32.7, 30.2, 29.8, 29.7 (2 C), 29.6 (2 C), 29.5, 28.48/28.43*, 27.5/26.8*, 26.1, 25.6, 25.3, 25.1, 24.4/23.1*, 23.0. HRMS: *m/z* calcd for $C_{37}H_{69}NO_8$ + Na: 678.4921; found: 678.4935.

Compound **18**: $[\alpha]_D$ –29.3 (*c* 0.3, $CHCl_3$) [Lit.[4b] $[\alpha]_D$ +37.6 (*c* 0.98, $CHCl_3$)]. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.95 (dt, *J* = 15.5, 7.0 Hz, 1 H), 5.80 (d, *J* = 15.6 Hz, 1 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 4.06 (br s, 1 H), 4.02–3.96 (m, 1 H), 3.95–3.81 (m, 3 H), 3.61 (br s, 1 H), 3.59–3.24 (m, 4 H), 2.50–2.26 (m, 1 H), 2.19 (q, *J* = 7.0 Hz, 2 H), 2.16–1.36 (m, 25 H), 1.35–1.21 (m, 33 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.7, 152.5/151.7*, 148.8, 121.4, 109.6, 93.7/93.2*, 82.3, 80.3/79.7*, 77.6, 71.3, 69.97/69.19*, 66.2, 65.6/65.3*, 60.1, 56.4/56.3*, 37.4, 35.0, 32.0, 30.0, 29.7, 29.4, 28.7/28.4*, 27.8, 27.4/26.7*, 26.0, 25.0, 24.3/23.0*, 22.9, 14.2. HRMS: *m/z* calcd for $C_{41}H_{73}NO_9$ + Na: 746.5183; found: 746.5188.