General synthetic strategy for clavaminols A, C and H

Barla Thirupathi, Yada Bharath, and Debendra K. Mohapatra*

Natural Products Chemistry Division, CSIR- Indian Institute of Chemical Technology
Hyderabad-500607, India

E-mail: mohapatra@iict.res.in

**Dedicated to Dr. J. S. Yadav on the occasion of his 65th birthday and
in appreciation of his outstanding contributions to synthetic organic chemistry**

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Abstract

A general and efficient synthetic strategy has been developed for the total syntheses of clavaminols A, C and H in 5 to 7 steps starting from (*R*)-Garners aldehyde following Grignard reaction, Corey-Bakshi-Shibata asymmetric reduction and selective acetylation as key steps with 42 to 59% overall yields, respectively.

Keywords: Clavaminols, sphingosine, cytotoxic, Garners aldehyde, CBS asymmetric reduction

Introduction

The marine natural products have played leading role for anticancer drug discovery. More than 70% of the drugs are now in clinical trials for cancer patients, either natural products or pharmacophore designed from the natural products.^{1,2} A thorough investigation of the chemical constituents of the Mediterranean ascidian *Clavelina phlegraea* led to the isolation of clavaminols A-N which are new marine sphingoid-type compounds.^{3,4} The structures of these molecules are generally related to the widely distributed amphiphilic sphingosine related long chain amino alcohols,⁵⁻⁷ the central structural element of sphingolipids; their carbon chain varies from C₁₂ to C₃₀ and few of them have also polyunsaturated variants.⁸⁻¹² Their structures were established by thorough analysis of spectroscopic data and chemical conversion. These compounds showed cytotoxic and pro-apoptotic activities against different cell lines A549 (lung carcinoma), T47D (breast carcinoma) and AGS (gastric carcinoma), including cell death through activation of the apoptotic machinery. Among them clavaminol A (Figure 1) had shown more cytotoxic activity with IC₅₀ near 5 µg/mL. Structurally, the 2-amino-3-alkanols isolated from *Clavelina phlegraea* were found to have (2*R*,3*S*)-configuration, which is opposite to that of the

well-known sphingolipids or other 2-amino-3-alkanols such as (2*S*,3*R*)-2-aminododecan-3-ol,¹³ an antifungal agent (against *Candida albicans* with MIC 30 µg/mL) isolated from *Clavelina oblonga* and (2*S*,3*R*)-2-aminotetradecan-3-ol, an inhibitor of cell proliferation isolated from *Spisula polynima*.¹⁴⁻¹⁶ Synthesis and complete biological profile of (2*S*,3*R*)-2-aminodecanols was well reported in literature.¹⁷⁻²⁰

1. R₁ = H; R₂ = H; R₃ = H; Clavaminol A
2. R₁ = Ac; R₂ = H; R₃ = H; Clavaminol C
3. R₁ = H; R₂ = Ac; R₃ = H; Clavaminol F
4. R₁ = Ac; R₂ = Ac; R₃ = H; Clavaminol I
5. R₁ = Ac; R₂ = H; R₃ = OH; Clavaminol H
6. R₁ = CHO; R₂ = H; R₃ = H; Clavaminol L

7. Clavaminol D

Figure 1: Structures of clavaminols.

Results and Discussion

These molecules are mostly long chain amino alcohols and their potent biological activity which ranges from antimicrobial activity to inhibition of cell proliferation through prevention of the formation of actin stress fibers in cultured cells,²¹⁻²⁹ attracted many natural products chemists. There are very few protocols reported for the synthesis of clavaminols. The first total synthesis of clavaminol A, C and H was achieved by Andrew Sutherland et al.,³⁰ starting from (*R*)-glycidol with an overall yield of 29% and confirmed absolute configuration as (2*R*,3*S*). An improved four step synthesis of long-chain *anti*-2-amino-3-alkanols was achieved by Huang and co-workers.³¹ In this context, we have thought of developing a general synthetic approach for the synthesis of all 2-amino-3-alkanols. Herein, we report the synthesis of clavaminols A, C and H from commercially available Garner's aldehyde^{32,33} in concise and high overall yields.

Scheme 1. Retrosynthetic analysis.

In our retrosynthetic perspective, we envisaged that the target molecules could be achieved from compound **8**, serving as the key intermediate in the present synthesis. The hydroxyl group at C3 of the natural products was planned to be introduced by diastereoselective nucleophilic addition on Garners aldehyde or by oxidation followed by asymmetric reduction using Corey-Bakshi-Shibata catalyst (Scheme 1).

Scheme 2: Synthesis of clavaminols A (**1**) and H (**5**): *Reagents and conditions:* (a) Nonylmagnesium bromide, THF, $-78\text{ }^{\circ}\text{C}$ - $0\text{ }^{\circ}\text{C}$, 30 min, 91%, (*syn/anti* = 1:3); (b) DMP, CH_2Cl_2 , $0\text{ }^{\circ}\text{C}$ -rt, 30 min, 96%; (c) (*R*)-CBS, THF, $-40\text{ }^{\circ}\text{C}$, 8 h, 92%; (d) CSA, MeOH, $0\text{ }^{\circ}\text{C}$ -rt, 4 h, 90%; (e) TsCl, Et_3N , CH_2Cl_2 , $0\text{ }^{\circ}\text{C}$ -rt, 5 h; (f) LiAlH_4 , THF, $-20\text{ }^{\circ}\text{C}$, 4 h, 79% over two steps; (g) Et_2O -HCl, $0\text{ }^{\circ}\text{C}$ -rt 10 h, 88%; (h) (1) TFA, CH_2Cl_2 - H_2O , $0\text{ }^{\circ}\text{C}$ -rt, 2 h; (2) AcCl, NaHCO_3 , CH_2Cl_2 - H_2O (1:1), $0\text{ }^{\circ}\text{C}$ -rt, 3 h, 85% (over two steps).

Accordingly, our synthesis was started from commercially available (*R*)-Garners aldehyde (**10**). Stereoselective addition of freshly prepared nonylmagnesium bromide on Garners aldehyde at $-78\text{ }^{\circ}\text{C}$ gave *syn* and *anti* in the ratio 1:3 (By HPLC).³⁴ The hydroxyl group present in compound **11** was smoothly converted to ketone **9** by using Dess-Martin periodinane (DMP) (Scheme 2).^{35,36} Stereoselective reduction of keto group was then undertaken. Here, we have screened different chelation controlled reducing agents to get good *anti* selectivity.³⁴ Among them (*R*)-CBS reductions gave good selectivity in 93:7 ratio (by HPLC) with 92% yield (Table 1). The acetonide group present in **11a** was then deprotected with CSA in methanol to afford **8** with 90% yield.

Table1. Chelation controlled reduction

Entry	Reagent ^a	Time (h)	Yield (%)	Ratio <i>anti/syn</i>
1	ZnBH ₄	3	94	80:20
2	NaBH ₄	2	89	65:35
3	K-Selectride	4	85	70:30
4	(<i>R</i>)-CBS	5	92	93:07

^aThe reaction was conducted under anhydrous and inert conditions.

Compound **8** was converted to compound **12** in two steps. In the first step, primary alcohol was selectively protected as tosylate,³⁷ followed by replacement of tosyl group with hydride in presence of LiAlH₄³⁸ afforded desired compound **12**. Deprotection of Boc group with HCl in ether afforded clavaminol A (**1**) in 88% yield. From intermediate **8**, clavaminol H (**5**) was prepared *in situ*, Boc-deprotection with TFA followed by selective *N*-acylation in presence of hydroxyl group with acetyl chloride in CH₂Cl₂-H₂O (1:1) with 85% yield.³⁹ Similarly, Clavaminol C (**2**) was prepared from **1** under the same reaction conditions as followed for the preparation of **5** from **8** (Scheme 3).

Scheme 3. Synthesis of clavaminols C (**2**) from clavaminol A (**1**): *Reagents and conditions:* (a) AcCl, NaHCO₃, CH₂Cl₂-H₂O (1:1), 0 °C-rt, 3 h, 89%.

Conclusions

The total synthesis of clavaminols A, C and H were achieved in an efficient manner starting from commercially available (*R*)-Garner's aldehyde in 5 to 7 steps with 42 to 59% overall yields, respectively. The key steps of the synthesis are Grignard reaction, chelation-controlled reduction

and selective acetylation reactions. Our protocol is highly general and flexible for the synthesis of other related natural products compared with earlier reports.

Experimental Section

General. All reactions were carried out under inert atmosphere, unless otherwise mentioned. Solvents were dried and purified by standard methods prior to use. The progress of all reactions was monitored by TLC using glass plates precoated with silica gel 60 F254 to a thickness of 0.5 mm. Column chromatography was performed on silica gel (60 mesh) using ethyl acetate and hexane as the eluents. Optical rotations were measured with Perkin Elmer P241 polarimeter and JASCO DIP-360 digital polarimeter at 27 °C. IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer. ¹H and ¹³C NMR spectra were recorded on a Variant Gemini 200 MHz, Bruker Avance 300 MHz, or Varian Inova 500 MHz spectrometer using TMS as an internal standard in CDCl₃, CD₃OD etc. Mass spectra were on Micromass VG-7070H for EI.

(*R*)-tert-Butyl 4-(1-hydroxydecyl)-2,2-dimethyloxazolidine-3-carboxylate (11). To a stirred solution of Garner's aldehyde **10** (6.0 g, 26.20 mmol) in anhydrous THF (100 mL) was added freshly prepared nonylmagnesium bromide (61 mL, 0.52M) at -78 °C under nitrogen atmosphere. The reaction mixture was stirred for 1 h at -78 °C when TLC showed completion of the reaction. The reaction mixture was quenched with saturated aqueous ammonium chloride (50 mL), extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine (150 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane 1:5) to furnish the desired compound **11** (8.5 g, 91%) as a colorless liquid. [α]_D²⁷ +22.4 (*c* 1.1, CHCl₃); IR (neat): 3451, 2926, 2855, 1700, 1391, 1255, 1174, 1066 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 4.18–3.48 (m, 4H), 1.62–1.53 (m, 3H), 1.49 (s, 12H), 1.28 (s, 10H), 0.89 (t, *J* 7.0 Hz, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃): 153.9, 93.9, 80.6, 72.3, 64.3, 62.1, 32.8, 31.7, 29.5, 29.1, 28.1, 26.3, 25.9, 25.2, 24.1, 22.4, 13.9 ppm; HRMS (ESI) *m/z* calcd. for C₂₀H₃₉NO₄ [M + Na]⁺ 380.27709, found 380.27713.

(*R*)-tert-Butyl 4-decanoyl-2,2-dimethyloxazolidine-3-carboxylate (9). To a stirred solution of alcohol **11** (5.1 g, 14.28 mmol) in anhydrous CH₂Cl₂ (50 mL) was added Dess-Martin periodinane (1.76 g, 28.56 mmol) at 0 °C under nitrogen atmosphere. After completion of the reaction (monitored by TLC), it was filtered through a Celite bed and washed thoroughly with CH₂Cl₂ (2 × 50 mL). The filtrate was washed with sodium thiosulphate (2 × 100 mL), then brine (2 × 100 mL) and dried over anhydrous Na₂SO₄, concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane 1:10) to furnish the desired compound **9** (4.8 g, 96%) as light yellow oil. [α]_D²⁷ +17.6 (*c* 1.0, CHCl₃); IR (neat): 2927, 2856, 1708, 1461, 1372, 1266, 1172, 1094, 850 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 4.44 (dd, *J* 2.3, 6.8 Hz, 1H), 4.32 (dd, *J* 2.3, 7.5 Hz, 1H), 4.14 (AB_q, *J* 9.1, 17.4 Hz, 1H), 3.90 (ddd, *J* 2.3, 3.0, 12.1 Hz, 1H), 2.54–2.45 (m, 2H), 1.62–1.56 (m, 3H), 1.50 (s, 9H), 1.26 (s, 16H), 0.88 (t,

J 6.8 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl_3): 208.0, 151.0, 94.7, 80.0, 65.3, 64.9, 38.1, 31.5, 29.0, 27.9, 24.9, 23.3, 22.3, 13.7 ppm; HRMS (ESI) m/z calcd. for $\text{C}_{20}\text{H}_{37}\text{NO}_4$ $[\text{M} + \text{Na}]^+$ 378.26151, found 378.26148.

(*R*)-tert-Butyl 4-((*S*)-hydroxydecyl)-2,2-dimethyloxazolidine-3-carboxylate (11a). To a stirred solution of (*R*)-CBS catalyst was added BH_3 -DMS (7.2 mL, 1M) at -40°C and stirred it for 45 min at same temperature. The solution of ketone **9** (2.5 g, 7.04 mmol) in THF (10 mL) was added to the reaction mixture and it was allowed to stir for 8 h at -40°C . TLC showed completion of the reaction. The reaction mixture was quenched with methanol (10 mL) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane 1:5) to furnish the desired compound **11a** (2.3 g, 92%) as a colorless liquid. $[\alpha]_{\text{D}}^{27} +10.2$ (c 2.5, CHCl_3); IR (neat): 3355, 2923, 2923, 1689, 1533, 1465, 1175, 1053 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 4.12–3.53 (m, 4H), 1.59 (s, 4H), 1.50 (s, 12H), 1.26 (s, 15H), 0.88 (t, J 6.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl_3): 151.3, 95.0, 80.4, 65.6, 65.2, 38.4, 31.8, 29.6, 29.2, 28.2, 26.1, 25.3, 24.7, 23.6, 23.0, 22.6, 14.0 ppm; HRMS (ESI) m/z calcd. for $\text{C}_{20}\text{H}_{40}\text{NO}_4$ $[\text{M} + \text{H}]^+$ 358.29558, found 358.29519.

tert-Butyl-(2*R*,3*S*)-1,3-dihydroxydodecan-2-yl-carbamate (8). To a stirred solution of compound **11a** (2.1 g, 5.88 mmol) in CH_2Cl_2 (30 mL) added CSA (catalytic amount) at 0°C stirred for 1 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with triethylamine and concentrated under reduced pressure. The crude product was purified by silica gel (ethyl acetate/hexane 1:5) to furnish the desired compound **8** (2.0 g, 90%) as a colorless liquid. $[\alpha]_{\text{D}}^{27} -3.5$ (c 1.3, CHCl_3); IR (neat): 3350, 2925, 2854, 1688, 1258, 1366, 1174, 1051 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3): δ 5.43 (d, J 7.5 Hz, 1H), 3.98 (dd, J 3.0, 10.6 Hz, 1H), 3.74–3.68 (m, 2H), 2.80 (AB_q, J 3.0, 27.5 Hz, 2H), 1.83 (br s, 1H), 1.44 (s, 9H), 1.27 (s, 14H), 0.88 (t, J 6.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, CDCl_3): 156.1, 79.6, 74.0, 62.4, 54.8, 34.3, 34.1, 31.8, 29.5, 29.3, 28.3, 25.9, 25.6, 22.6, 14.0 ppm; HRMS (ESI) m/z calcd. for $\text{C}_{17}\text{H}_{36}\text{NO}_4$ $[\text{M} + \text{H}]^+$ 318.26428, found 318.26389.

tert-Butyl-(2*R*,3*S*)-3-hydroxydodecan-2-ylcarbamate (12). To a stirred solution of 1,3-diol **8** (2.0 g, 6.30 mmol) in CH_2Cl_2 (30 mL), was added triethyl amine (1.63 mL, 12.63 mmol) at 0°C followed by tosyl chloride (1.38 g, 6.94 mmol) and catalytic amount of dibutyltin oxide. The mixture was stirred for 4 h at room temperature after completion (monitored by TLC), it was quenched with water (10 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3×25 mL). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane 1:5) to furnish the desired compound was immediately used next reaction.

To a slurry of LiAlH_4 (0.41 g, 10.7 mmol) THF (10 mL), was added tosylated compound (2.52 g, 5.35 mmol) in THF (5 mL) at -20°C and stirred for 5 h at same temperature. After completion of the reaction (monitored by TLC), it was quenched with saturated aqueous ammonium chloride solution (20 mL) and filtered through a Celite pad. It was thoroughly washed with ethyl acetate (2×20 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate

(3 x 40 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel (ethyl acetate/hexane 1:5) to furnish the desired compound **12** (1.33 g, 79% over two steps) [α]_D²⁷ +2.7 (*c* 1.2, CHCl₃); IR (Neat): 3438, 2926, 2855, 1689, 1504, 1032 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 4.79 (AB_q, *J* 8.3, 24.9 Hz, 1H), 3.64 (m, 2H), 3.48 (br s, 1H), 2.30 (br s, 1H), 1.44 (s, 9H), 1.26 (s, 13H), 1.17 (d, *J* 6.8 Hz, 3H), 0.88 (t, *J* 6.0 Hz, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃): 156.2, 74.8, 74.3, 50.2, 34.1, 33.4, 32.7, 31.8, 29.6, 29.2, 28.3, 26.0, 25.6, 22.6, 14.1 ppm; HRMS (ESI) *m/z* calcd. for C₁₇H₃₅NO₃ [M]⁺ 301.26174, found 301.26148.

(2R,3S)-2-Aminododecan-3-ol (Clavaminol A) (1). HCl ether (6.6 mL, 6.63 mmol, 1M) was added compound **12** (0.5 g, 1.66 mmol) at 0 °C and stirred for 2 h at room temperature. After completion of the reaction (monitored by TLC), the solvent was evaporated under reduced pressure and the resulting oil dissolved in ethyl acetate (20 mL). Aqueous ammonia solution (10 mL) was added at 0 °C and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 x 15 mL). The combined organic layer was washed with NaHCO₃ (40 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (MeOH/CH₂Cl₂ 1:10) to yield **1** (0.29 g, 88%) as a white amorphous solid. mp 107–108 °C; [α]_D²⁷ -4.4 (*c* 1.2, MeOH); IR (KBr): 3395, 2925, 2854, 1608, 1500, 1152, 1028, 723 cm⁻¹; ¹H NMR (300 MHz, CD₃OD): δ 3.68–3.74 (br m, 1H), 3.30–3.24 (br m, 1H), 1.65–1.28 (m, 16H), 1.22 (d, *J* 5.9 Hz, 3H), 0.90 (t, *J* 7.8 Hz, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃): 71.6, 52.6, 34.1, 33.1, 30.7, 30.6, 30.5, 27.0, 23.8, 14.5, 12.1 ppm; HRMS (ESI) *m/z* calcd. for C₁₂H₂₈NO [M + H]⁺ 202.21654, found: 202.21631.

N-((2R,3S)-1,3-Dihydroxydodecan-2-yl)acetamide (clavaminol H) (5). A solution of TFA/H₂O (3.1 mL, 0.31 mmol) was added to **8** (100 mg, 0.31 mmol) in CH₂Cl₂ (5 mL) and the resulting mixture stirred at room temperature for 3 h. After completion of the reaction (as determined by TLC), the solvent was evaporated under reduced pressure and the resulting reddish oil dissolved in ethyl acetate (10 mL). The organic phase was washed with NaHCO₃, dried over Na₂SO₄ and concentrated under reduced pressure. The red oil (0.05 g, 0.24 mmol) so obtained was dissolved in CH₂Cl₂–H₂O (1:1) (10 mL) and NaHCO₃ (204 mg, 2.4 mmol) was added followed by acetyl chloride (0.02 mL, 0.29 mmol). After completion of reaction (monitored by TLC), water (5 mL) was added to it. The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layer dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane 1:6) to furnish the desired compound **5** (85% over two steps) as a white amorphous solid. mp 108–110 °C; [α]_D²⁷ +3.1 (*c* 1.0, MeOH); IR (KBr): 3294, 2919, 2851, 1649, 1551, 1373, 1090, 1046 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 6.58 (br d, *J* 7.5 Hz, 1H), 3.98 (dd, *J* 3.0, 11.3 Hz, 1H), 3.87–3.70 (m, 3H), 3.13 (br s, 1H), 2.04 (s, 3H), 1.59–1.43 (m, 2H), 1.38–1.21 (m, 14H), 0.88 (t, *J* 6.0 Hz, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃): 170.7, 73.9, 62.2, 53.9, 34.4, 31.8, 29.7, 29.5, 29.3, 26.0, 23.4, 22.6, 14.1 ppm; HRMS (ESI) *m/z* calcd. for C₁₄H₂₉NO₃Na [M + Na]⁺ 282.20369, found 282.20396.

***N*-((2*R*, 3*S*)-3-Hydroxydodecan-2-yl) acetamide (Clavaminol C) (2).** To a stirred solution of compound **1** (0.05 g, 0.24 mmol) in CH₂Cl₂–H₂O (1:1) (10 mL), was added solid NaHCO₃ (104 mg, 1.2 mmol) followed by acetyl chloride (0.02 mL, 0.29 mmol). After completion of the reaction (monitored by TLC), water (5 mL) was added. The organic layer was separated and the aqueous layer extracted with CH₂Cl₂ (3 × 15 mL). The combined organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel (ethyl acetate/hexane 1:6) to furnish the desired compound **2** (53 mg, 89%) as white amorphous solid. mp 102–105 °C; [α]_D²⁷ +11.8 (*c* 1.7, MeOH); IR (KBr): 3286, 3095, 2919, 2852, 1745, 1645, 1553, 1373, 1225, 1023 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 5.98 (br d, *J* 6.8 Hz, 1H), 4.10–3.88 (m, 2H), 3.64 (m, 1H), 2.74 (br s, 1H), 1.99 (s, 3H), 1.50–1.38 (m, 2H), 1.36–1.21 (m, 13H), 1.09 (d, *J* 6.8 Hz, 3H), 0.88 (t, *J* 6.8 Hz, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃): 170.3, 74.4, 49.4, 33.5, 31.8, 29.6, 29.5, 29.2, 26.0, 25.6, 23.3, 22.6, 14.0, 13.7 ppm; HRMS (ESI) *m/z* calcd. for C₁₄H₃₀NO₂ [M + H]⁺ 244.22698, found: 244.22711.

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References

1. Cragg, G. M.; Newman, D. J. *Biochim. Biophys. Acta* **2013**, 3670.
<http://dx.doi.org/10.1016/j.bbagen.2013.02.008>
2. Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2012**, 75, 311 and references therein.
<http://dx.doi.org/10.1021/np200906s>
3. Aiello, A.; Fattorusso, E.; Giordano, A.; Menna, M.; Navarrete, C.; Munoz, E. *Tetrahedron* **2009**, 65, 4384.
<http://dx.doi.org/10.1016/j.tet.2009.03.056>
4. Aiello, A.; Fattorusso, E.; Giordano, A.; Menna, M.; Navarrete, C.; Munoz, E. *Bioorg. Med. Chem.* **2007**, 15, 2920.
<http://dx.doi.org/10.1016/j.bmc.2007.02.015>
5. Koskinen, M.; Koskinen, A. M. P.; *Synthesis* **1998**, 1075.
<http://dx.doi.org/10.1055/s-1998-4494>
6. Howell, A. R.; So, R. C.; Richardson, S. K. *Tetrahedron* **2004**, 60, 11327.
<http://dx.doi.org/10.1016/j.tet.2004.09.056>

7. Pruett, S. T.; Bushnev, A.; Hagedorn, K.; Adiga, M.; Hynes, A. C.; Sullards, M. C.; Liotta, D. C.; Merrill, H. M. Jr. *J. Lipids Res.* **2008**, *49*, 1621.
<http://dx.doi.org/10.1194/jlr.R800012-JLR200>
8. Clark, R. J.; Garson, M. J.; Hooper, J. N. A. *J. Nat. Prod.* **2001**, *64*, 1568.
<http://dx.doi.org/10.1021/np010246x>
9. Makarieva, T. N.; Denisenko, V. A.; Stonik, V. A.; Milgrom, J. M.; Rashkes, Y. V. *Tetrahedron Lett.* **1989**, *30*, 6581.
[http://dx.doi.org/10.1016/S0040-4039\(01\)89027-4](http://dx.doi.org/10.1016/S0040-4039(01)89027-4)
10. Molinski, T. F.; Makarieva, T. N.; Stonik, V. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 4076.
[http://dx.doi.org/10.1002/1521-3773\(20001117\)39:22<4076::AID-ANIE4076>3.0.CO;2-D](http://dx.doi.org/10.1002/1521-3773(20001117)39:22<4076::AID-ANIE4076>3.0.CO;2-D)
11. Nicholas, G. M.; Hong, T. W.; Molinski, T. F.; Lerch, M. L.; Cancilla, M. T.; Lebrilla, C. B. *J. Nat. Prod.* **1999**, *62*, 1678.
<http://dx.doi.org/10.1021/np990190v>
12. Nicholas, G. M.; Molinski, T. F. *J. Am. Chem. Soc.* **2000**, *122*, 4011.
<http://dx.doi.org/10.1021/ja994215o>
13. Kossuga, M. H.; Macmillan, J. B.; Rogers, E. W.; Molinski, T. F.; Nascimento, G. G. F.; Rocha, R. M.; Berlinck, R. G. S. *J. Nat. Prod.* **2004**, *67*, 1879.
<http://dx.doi.org/10.1021/np049782q>
14. Cuadros, R.; Garcini, E. M.; Wandosell, F.; Faircloth, G.; Fernández-Sousa, J. M.; Avila, J. *Cancer Lett.* **2000**, *152*, 23.
[http://dx.doi.org/10.1016/S0304-3835\(99\)00428-0](http://dx.doi.org/10.1016/S0304-3835(99)00428-0)
15. Shaw, A. K.; Ghosal, P. *Tetrahedron Lett.* **2010**, *51*, 4140.
<http://dx.doi.org/10.1016/j.tetlet.2010.05.146>
16. Dinda, S. K.; Das, S. K.; Panda, G. *Tetrahedron* **2010**, *66*, 9304.
<http://dx.doi.org/10.1016/j.tet.2010.09.018>
17. Reddy, T. V. K.; Devi, B. L. A. P.; Prasad, R. B. N.; Poornima, M.; Kumar, C. G. *Bio. Org. Med. Chem. Lett.* **2010**, *22*, 4678.
<http://dx.doi.org/10.1016/j.bmcl.2012.05.082>
18. Clader, E. E. D.; Zaed, A. M.; Sutherland, A.; *J. Org. Chem.* **2013**, *78*, 7223.
<http://dx.doi.org/10.1021/jo401211j>
19. Kumar, J. N.; Das, B.; *Tetrahedron Lett.* **2013**, *54*, 3865.
<http://dx.doi.org/10.1016/j.tetlet.2013.05.029>
20. Pandey, M.; Chowdhury, P. S.; Dutta, A. K.; Kumar, P.; Pal, S. *RSC Adv.* **2013**, *3*, 15442.
<http://dx.doi.org/10.1039/c3ra43048k>
21. Gulavita, N. K.; Scheuer, P. J. *J. Org. Chem.* **1989**, *54*, 366.
<http://dx.doi.org/10.1021/jo00263a019>
22. Makarieva, T. N.; Denisenko, V. A.; Stonik, V. A. *Tetrahedron Lett.* **1989**, *30*, 6581.
[http://dx.doi.org/10.1016/S0040-4039\(01\)89027-4](http://dx.doi.org/10.1016/S0040-4039(01)89027-4)
23. Jiménez, C.; News, P. *J. Nat. Prod.* **1990**, *53*, 978.
<http://dx.doi.org/10.1021/np50070a033>

24. Jared-Erijman, E. A.; Bapat, C. P.; Lithgow-Bertelloni, A.; Rinehart, K. L.; Sakai, R. *J. Org. Chem.* **1993**, *58*, 5732.
<http://dx.doi.org/10.1021/jo00073a036>
25. Searle, P. A.; Molinski, T. F. *J. Org. Chem.* **1993**, *58*, 7578.
<http://dx.doi.org/10.1021/jo00078a045>
26. Casapullo, A.; Fontana, A.; Cimino, G. *J. Org. Chem.* **1996**, *61*, 7415.
<http://dx.doi.org/10.1021/jo9604200>
27. Devijver, C.; Salmoun, M.; Daloz, D.; Braekman, J. C.; De Weerd, W. H.; De Kluijver, M. J.; Gomez, R. *J. Nat. Prod.* **2000**, *63*, 978.
<http://dx.doi.org/10.1021/np000081c>
28. Garrido, L.; Zubia, E.; Ortega, M. J.; Naranjo, S.; Salva, J. *Tetrahedron* **2002**, *57*, 4579.
[http://dx.doi.org/10.1016/S0040-4020\(01\)00372-6](http://dx.doi.org/10.1016/S0040-4020(01)00372-6)
29. Clark, R. J.; Garson, M. J.; Hooper, J. N. A. *J. Nat. Prod.* **2001**, *64*, 1568.
<http://dx.doi.org/10.1021/np010246x>
30. Zaed, A. M.; Sutherland, A. *Org. Biomol. Chem.* **2011**, *9*, 8030.
<http://dx.doi.org/10.1039/c1ob06060k>
31. Chen, B. S.; Yang, L. H.; Ye, J. L.; Huang, T.; Ruan, Y. P.; Fu, J.; Huang, P. Q. *Eur. J. Med. Chem.* **2011**, *46*, 5480.
<http://dx.doi.org/10.1016/j.ejmech.2011.09.010>
32. Liang, X.; Anders, Ch. J.; Bols, M. *J. Chem. Soc. Perkin Trans. 1*, **2001**, 2136.
<http://dx.doi.org/10.1039/b101054i>
33. Williams, L.; Zhang, Z.; Shao, F.; Carroll, P. J.; Joullie, M. M. *Tetrahedron* **1996**, *52*, 11673.
[http://dx.doi.org/10.1016/0040-4020\(96\)00672-2](http://dx.doi.org/10.1016/0040-4020(96)00672-2)
34. Datta, A.; Kumar, J. S. R. Roy, S. *Tetrahedron* **2001**, *57*, 1169.
[http://dx.doi.org/10.1016/S0040-4020\(00\)01113-3](http://dx.doi.org/10.1016/S0040-4020(00)01113-3)
35. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
<http://dx.doi.org/10.1021/jo00170a070>
36. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
<http://dx.doi.org/10.1021/ja00019a027>
37. Martinelli, M. J.; Nayer, N. K.; Moher, E. D.; Dhonkte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett.* **1999**, *1*, 447.
<http://dx.doi.org/10.1021/ol990658l>
38. Tosylate compound was unstable and immediately used for the next reaction.
39. Mina, J. G.; Mosely, J. A.; Ali, H. Z.; Denny, P. W.; Steel, P. G. *Org. Biomol. Chem.* **2011**, *9*, 1823.
<http://dx.doi.org/10.1039/c0ob00871k>