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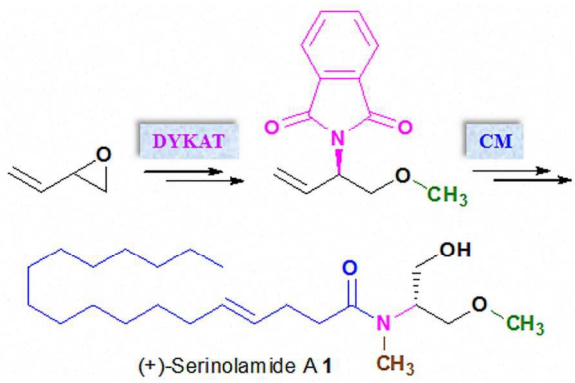

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PAPER

Enantioselective total synthesis of (+)-serinolamide A‡

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A short and highly efficient enantioselective synthetic approach to (+)-serinolamide A **1** from racemic butadiene monoepoxide as a starting material is described. The synthesis utilizes the palladium catalyzed Trost's Dynamic Kinetic Asymmetric Transformation (DYKAT) and cross-metathesis (CM) as key steps.

Keywords: Cross-metathesis, DYKAT, asymmetric, total synthesis, natural products.

Introduction

The endocannabinoid lipid (+)-serinolamide A **1** was isolated from the marine cyanobacteria *Lyngbya majuscula* collected in Papua New Guinea, and represents the newest addition to the known cannabinomimetic natural products.[1] (+)-Serinolamide A **1** showed selectivity for the CB_1 cannabinoid receptor (K_i = 1.3 μM, >5-fold) and exhibits moderate agonist effect (Figure 1).

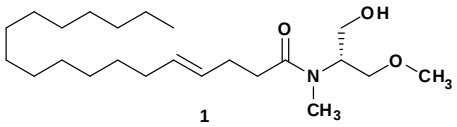

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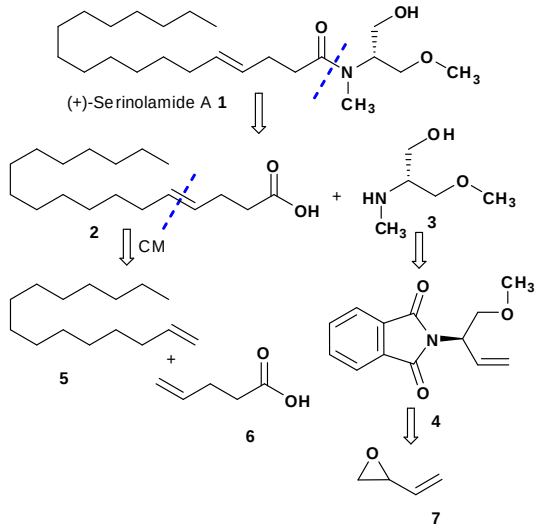
Figure 1. Structure of (+)-serinolamide A **1**.

(+)-Serinolamide A **1** has been a synthetic target of considerable interest due to its long chain fatty acid bonded to a chiral serinol derivative with an array of functionalities. Very recently, Y-Q. Wang and co-workers reported the first total synthesis of (+)-serinolamide A **1** in nine steps starting from chiral starting material L-serine *via* Kuhn's methylation, Wittig olefination and acid-amine coupling reactions.[2] To avoid possible racemization, Kuhn method[3a] for *O*-methylation reaction is generally performed under neutral conditions involving MeI and Ag_2O, and requires longer reaction time (3–5 days) for better yield.[3b-c] Herein, we wish to report a new, short and highly efficient synthetic strategy for (+)-serinolamide A **1** employing Trost's DYKAT and cross-metathesis as key steps. We have also developed an efficient approach for *O*-methylation employing MeI and NaH as a base which would eliminate the problem of partial racemization and shorten the reaction time.

Results and discussion

Our retrosynthetic approach for the synthesis of (+)-serinolamide A **1** is outlined in Scheme 1. Accordingly, we envisioned that the (+)-serinolamide A **1** could be obtained from the two fragments, the long chain fatty acid **2** and serinol derivative **3**. The fatty acid fragment **2** could be obtained from pentadec-1-ene **5** and pent-4-enoic acid **6** *via* cross-metathesis. The phthalimide derivative **4** was visualized as a synthetic intermediate from which serinol derivative **3** could be synthesized. Terminal double bond of derivative **4** on standard organic transformation *viz.* phthalimide cleavage, oxidative cleavage and reduction could give the serinol derivative **3**. Enantiopure phthaloyl methyl ether derivative **4**



Scheme 1. Retrosynthetic approach to (+)-serinolamide A **1**.

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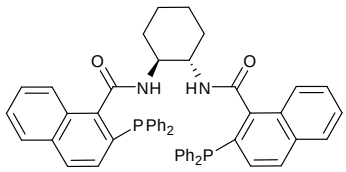
‡ *Dedicated to Dr. Pradeep Kumar in recognition of his seminal contributions to so many aspects of organic chemistry.*

† *Electronic Supplementary Information (ESI) available: Copies of ^{1}H and ^{13}C NMR spectra of compounds **1-2, 4** and **8-9**. See DOI: 10.1039/x0xx00000x*

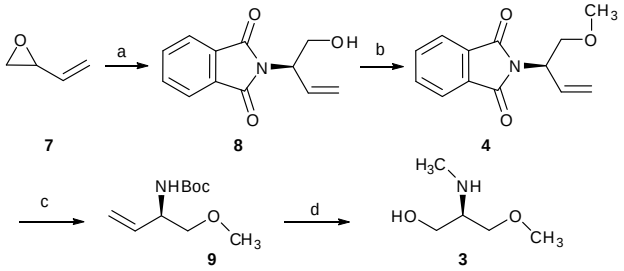


(*S*,*S*)-DACH

Figure 2: (*S*,*S*)-*N*,*N*'-1,2-Cyclohexanediylbis[2-(diphenylphosphino)-1-naphth-amide].

in turn could be easily prepared by the racemic butadiene monoepoxide **7** by means of Trost's DYKAT followed by methylation. The (*S*)- and (*R*)-configuration of the derivative **4** could be simply manipulated by changing the chiral ligand (*R*,*R*)-DACH and (*S*,*S*)-DACH (Figure 2), respectively, in the Trost's DYKAT step.

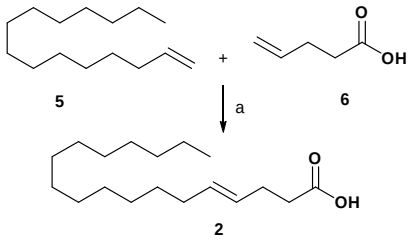
The synthesis of (+)-serinolamide A **1** started from the commercially available racemic starting material butadiene monoepoxide **7**, which can also be easily synthesized from silver-catalyzed oxidation of 1,3-butadiene (Scheme 2).[4] Deracemisation of butadiene monoepoxide **7** in highly regio- and enantioselective fashion in presence of palladium catalysed Trost's DYKAT with 1.2 mol % (*S*,*S*)-DACH and 0.4 mol % $[\eta^3\text{-}C_3H_5PdCl]_2$, phthalimide and base Na_2CO_3 furnished asymmetric allylic alkylation (AAA) derivative phthaloyl alcohol **8** as a single enantiomer in 99% yield with 99% ee {$[\alpha]_D^{25}$ = +66.0 (*c* 1, $CHCl_3$)} [Lit.[5] $[\alpha]_D^{25}$ = +65.9 (*c* 1, $CHCl_3$)].



Scheme 2 Reagents and conditions: (a) Phthalimide, Na_2CO_3, 1.2 mol % (*S*,*S*)-DACH, 0.4 mol % $[\eta^3\text{-}C_3H_5PdCl]_2$, dry CH_2Cl_2, rt, 14 h, 99%; (b) MeI, NaH, DMF, 0 °C to rt, 6 h, 91%; (c) i) $NH_2NH_2.H_2O$, isopropyl alcohol, 0 °C to rt, 2 h; (ii) $(Boc)_2O$, $NaHCO_3$, THF:H_2O (1:1) v/v, rt, 12 h, 87% (over two steps); (d) i) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane:water (3:1) v/v, rt, 2 h; ii) $LiAlH_4$, THF, 0 °C to reflux, 12 h.

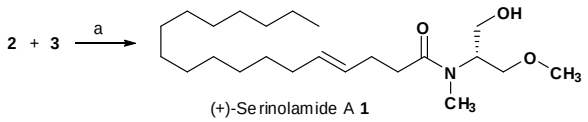
With enantiomerically pure alcohol **8** in hand, we then subjected it to *O*-methylation with MeI in presence of NaH which furnished the methyl ether **4** in 91% yield. Our next aim was to carry out the alcohol formation at the terminal double bond site and *N*-methylation at 2-aza site. To this end, one pot cleavage of phthalimide group of (*R*)-**4** with hydrazine mono-hydrate in 2-propanol followed by treatment of the resulting free amine with $(Boc)_2O$ in the presence of $NaHCO_3$ in THF:H_2O (1:1) furnished the Boc protected derivative (*R*)-**9** in 87% yield. Finally, oxidative cleavage of terminal double bond in presence of OsO_4 and sodium periodate[6] followed by concomitant reduction of aldehyde and *N*-Boc group with $LiAlH_4$ under reflux condition afforded the serinol derivative (*R*)-**3** which was used for coupling with acid **2** without purification.

On the other hand, the cross-metathesis[7] was undertaken with confidence between pentadec-1-ene **5** and 4-pentenoic acid **6** in presence of a small amount (5 mol %) of Grubbs'[8] second generation catalyst. The reaction proceeded smoothly, and the desired coupling product **2** was obtained in 95% yield with an impressive *E*/*Z* ratio (95:5). The homocoupling product of **6** was not observed by ^1H NMR. In this case the use of $Ti(O^iPr)_4$ or other additive was not necessary to obtain excellent results (Scheme 3).



Scheme 3 Reagents and conditions: (a) Grubbs' second generation catalyst (5 mol %), CH_2Cl_2, 40 °C, 12 h, 95%.

With long chain fatty acid **2** and serinol derivative **3** in hand, we then subjected it to acid amine coupling reaction in presence of ((1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC), 1-Hydroxy-1H-benzotriazole (HOBt) and *N*,*N*-Diisopropylethylamine (DIPEA) which afforded the target compound (+)-serinolamide A **1** in 65% yield $[\alpha]_D^{25}$ = +1.97 (*c* 0.18, $CHCl_3$) [Lit.[2] $[\alpha]_D^{20}$ = +1.98 (*c* 0.18, $CHCl_3$)]. The physical and spectroscopic data of (+)-serinolamide A **1** were in full agreement with those documented in the literature.



Scheme 4 Reagents and conditions: (a) EDC, HOBt, DIPEA, CH_2Cl_2, rt, 12 h, 65%.

In conclusion, a simple, flexible and highly efficient enantioselective synthesis of (+)-serinolamide A **1** has been developed. The overall yield for (+)-serinolamide A **1** was 51% in five steps. The merits of this synthesis are high regio- and enantioselectivity with high yielding reaction steps. Moreover, the synthetic strategy described has significant potential for stereochemical variations at C-2 position and further extension to other stereoisomers.

Experimental

The solvents and chemicals were purchased from Merck and Sigma Aldrich chemical company. Solvents and reagents were purified and dried by standard methods prior to use. All reactions were carried out under argon or nitrogen in oven-dried glassware using standard glass syringes and septa.

Progress of the reactions was monitored by TLC using precoated aluminium plates of Merck kieselgel 60 F254. Column chromatography was performed on silica gel (60-120 and 100-200 mesh) using a mixture of n-hexane and ethyl acetate. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise mentioned) on JEOL ECS operating at 400 and 100 MHz, respectively. Chemical shifts are reported in δ (ppm), referenced to TMS. Optical rotations were measured on automatic polarimeter AA-65. HRMS were recorded on Agilent 6530 Accurate-Mass Q-TOF using Electron Spray Ionization. IR spectra were recorded on Agilent resolution Pro 600 FT-IR spectrometer, fitted with a beam-condensing ATR accessory.

(*R*)-2-(Isoindolin-2-yl)but-3-en-1-ol, 8

A mixture of π-allylpalladium chloride dimer 0.4 mol % (14.6 mg, 0.04 mmol), (*S*,*S*)-DACH ligand 1.2 mol % (94.6 mg, 0.12 mmol), Na_2CO_3 (53 mg, 0.50 mmol) and phthalimide (1.47 g, 10 mmol) in 80 mL of dry CH_2Cl_2 was purged with nitrogen for 1 h. The resulting mixture was stirred for 10 minutes at room temperature to which butadiene monoepoxide **7** (810 μL, 10 mmol) was added. The resulting mixture was stirred at room temperature under nitrogen for 14 h, concentrated *in vacuo* and purified by silica gel column chromatography using EtOAc/hexane (3:7) as eluent furnished 2.16 g (99%) yield of (*R*)-**8** as a crystalline white solid. Mp 62-63 °C; [R_f = 0.21, EtOAc/hexane 3:7 v/v]; $[\alpha]_D^{25}$ = +66.01 (*c* 1.0, $CHCl_3$) [Lit.[5] $[\alpha]_D^{25}$ = +65.9 (*c* 1.0, $CHCl_3$)]; IR (KBr): *ν* 3517, 1755, 1695, 1656, 1611, 1475 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.85 (dd, *J* = 5.5, 2.8 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.2 Hz, 2H), 6.14 (ddd, *J* = 17.4, 10.6, 6.9 Hz, 1H), 5.30 (d, *J* = 0.9 Hz, 1H), 5.27 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.91-4.96 (m, 1H), 4.15 (ddd, *J* = 16.1, 11.4, 8.2 Hz, 1H), 3.97 (ddd, *J* = 11.9, 7.3, 3.6 Hz, 1H), 2.76 (dd, *J* = 8.2, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 168.5, 134.2, 131.9, 131.7, 123.4, 118.8, 62.8, 55.9.

(*R*)-2-(1-Methoxybut-3-en-2-yl)isoindoline, 4

To a solution of compound **8** (2.0 g, 9.2 mmol) in dry DMF (25 mL) was added NaH (442 mg, 18.4 mmol, 60% dispersion in mineral oil) at 0 °C in one portion, then MeI (1.73 mL, 27.6 mmol) was added to the reaction mixture at above temperature. The resulting mixture was allowed to warm at rt and stirred for 6 h. After completion of reaction monitored by TLC, the reaction mixture was quenched with cold H_2O, extracted with diethyl ether (3 x 20 mL) and dried over anhydrous $MgSO_4$. The organic layer was then concentrated under reduced pressure and purified by silica gel column chromatography using EtOAc/hexane (1:9) as eluent to afford 1.93 g (91%) yield of (*R*)-**4** as a crystalline white solid. [R_f = 0.56, EtOAc/hexane 3:7 v/v]; $[\alpha]_D^{25}$ = +55.17 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2): *ν* 1772, 1711, 1471, 1381 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.84 (dd, *J* = 5.5, 3.2 Hz, 2H), 7.72 (dd, *J* = 5.5, 2.8 Hz, 2H), 6.16 (ddd, *J* = 17.4, 10.6, 7.3 Hz, 1H), 5.32 (td, *J* = 17.4, 1.0 Hz, 1H), 5.27 (td, *J* = 10.6, 1.4 Hz, 1H), 5.01-5.07 (m, 1H), 4.05-4.15 (m, 1H), 3.64 (dd, *J* = 10.08, 5.96 Hz, 1H), 3.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 168.1, 133.9, 132.1, 131.9, 123.2, 119.0, 71.3, 58.7, 52.9; HRMS (ESI-TOF) m/z calcd for $C_{13}H_{13}NO_3Na$ [M + Na]$^+$ 254.0793, found 254.0793.

(*R*)-*tert*-Butyl 1-methoxybut-3-en-2-ylcarbamate, 9

To a solution of compound (*R*)-**4** (1.0 g, 4.32 mmol) in 10 mL of isopropyl alcohol was added hydrazine monohydrate (0.25 mL, 5.18 mmol) at 0 °C under nitrogen atmosphere. The reaction mixture was stirred at rt for 2 h. Then 30 mL of 6N aqueous hydrochloric acid was added and the reaction mixture was heated at reflux (80 °C) for 1 h. After cooling to 0 °C, the reaction mixture was filtered through glass wool to remove the phthalhydrazide. The crude solution was neutralized by sodium bicarbonate. Then 15 mL THF was added to the resulting solution followed by di-*tert*-butyl dicarbonate (1.89 g, 8.64 mmol), sodium bicarbonate (1.08 g, 12.96 mmol) and stirred for 12 h at rt. The reaction mixture was quenched by addition of water, extracted with ethyl acetate (3 x 20 mL) and dried over anhydrous $MgSO_4$. The organic layer was then concentrated *in vacuo* and purified by silica gel column chromatography using EtOAc/*n*-hexane (1:9) as eluent to furnish 750 mg (87%) yield of (*R*)-**9** as a colorless liquid. [R_f = 0.42, EtOAc/hexane 2:8 v/v]; $[\alpha]_D^{25}$ = +18.76 (*c* 1.0, $CHCl_3$); IR (CH_2Cl_2): *ν* 2977, 2930, 1685, 1456 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.82 (ddd, *J* = 15.6, 10.5, 5.0 Hz, 1H), 5.24 (td, *J* = 17.4, 1.4 Hz, 1H), 5.18 (td, *J* = 10.5, 1.4 Hz, 1H), 4.93 (brs, 1H), 4.29 (brs, 1H), 3.45 (d, *J* = 4.6 Hz, 2H), 3.35 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 155.2, 136.1, 115.3, 79.1, 74.3, 58.8, 52.1, 28.1; HRMS (ESI-TOF) m/z calcd for $C_{10}H_{19}NO_3Na$ [M + Na]$^+$ 224.1263, found 224.1261.

(*E*)-Octadec-4-enoic acid, 2

To a solution of pentadec-1-ene **5** (500 mg, 2.38 mmol) and 4-pentenoic acid **6** (48 mg, 48 μL, 0.48 mmol) in dry CH_2Cl_2 (100 mL) was added Grubbs' second generation catalyst (20 mg, 0.02 mmol, 5 mol %). The mixture was stirred at 40 °C for 12 h under argon atmosphere. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography using EtOAc/hexane (1:9) as eluent to furnish 128 mg (95%) yield of **2** as a white solid. [R_f = 0.25, EtOAc/hexane 2:8 v/v]; IR (KBr): *ν* 3420, 2900, 2820, 1710, 1460, 1280, 1220 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 5.48 (td, *J* = 15.1, 6.4 Hz, 1H), 5.39 (td, *J* = 15.1, 6.0 Hz, 1H) 2.42 (t, *J* = 6.9 Hz, 2H), 2.31 (m, 2H), 1.96 (m, 2H), 1.26 (m, 22H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 179.7, 132.2, 127.4, 32.5, 31.9, 29.7, 29.6, 29.5, 29.4, 29.1, 27.6, 22.7, 14.1.

(+)-Serinolamide A, 1

To a solution of compound (*R*)-**9** (120 mg, 0.6 mmol) in dioxane-water (3:1, 8 mL) was added 2,6-lutidine (0.14 mL, 1.2 mmol), OsO_4 (0.1 M solution in toluene, 0.12 mL, 0.01 mmol) and $NaIO_4$ (257 mg, 1.2 mmol). The reaction was stirred at 25 °C for 2 h. After completion of reaction, water (5 mL) and CH_2Cl_2 (15 mL) were added. The organic layer was separated, and the water layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with brine and dried over anhydrous $MgSO_4$, concentrated *in vacuo* to give crude aldehyde. The aldehyde obtained was dissolved in anhydrous THF (8 mL) and lithium aluminium hydride (140 mg, 3.6 mmol) was added at 0 °C under N_2 atmosphere. The reaction mixture was stirred at the same temperature under N_2 for additional

1h, then warmed up to reflux conditions and stirred for 11 h. The solution was quenched with 10% NaOH and extracted with ethyl acetate and dried over anhydrous $MgSO_4$. The organic layer was then concentrated *in vacuo* to afford serinol (*R*)-**3** which was used for coupling reaction without further purification due to high polar nature of (*R*)-**3**.

The residue (*R*)-**3** obtained above was dissolved in CH_2Cl_2 (3 mL) and added to a solution of (*E*)-octadec-4-enoic acid **2** (100 mg, 0.35 mmol), EDC (181 mg, 0.945 mmol), HOBt (76 mg, 0.56 mmol), and DIPEA (0.49 mL, 2.8 mmol) in CH_2Cl_2 (5 mL) at 0 ^oC. The reaction mixture was warmed to room temperature and stirred for 12 h. Then CH_2Cl_2 was added and the mixture was washed with water (5 mL) and brine (5 mL). The organic layer was dried over anhydrous $MgSO_4$, concentrated under reduced pressure and purified by silica gel column chromatography using EtOAc/hexane (1:1) as eluent to furnish 88 mg (65%) yield of (*R*)-**1** as a yellow liquid [R_f = 0.42, EtOAc]; {$[\alpha]_D^{25}$ = +1.97 (*c* 0.18, $CHCl_3$)} [Lit.[2] {$[\alpha]_D^{20}$ = +1.98 (*c* 0.18, $CHCl_3$)}]; IR (KBr): ν 3421, 2915, 2866, 1631, 1411, 1285, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.43-5.46 (m, 2H), 4.44-4.46 (m, 1H), 3.71-3.77 (m, 2H), 3.62-3.67 (m, 1H), 3.55 (dd, *J* = 10.50, 5.00 Hz, 1H), 3.46 (d, *J* = 6.4 Hz, 1H), 3.33 (s, 3H), 3.01 (s, 3H), 2.39-2.47 (m, 2H), 2.29-2.34 (m, 2H), 1.96 (d, *J* = 5.2Hz, 2H), 1.25-1.45 (m, 22H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 131.6, 128.4, 70.9, 61.8, 58.9, 57.1, 34.5, 33.3, 32.5, 31.9, 29.6, 29.5, 29.3, 29.2, 28.3, 22.6, 14.1; HRMS (ESI-TOF) m/z calcd for $C_{23}H_{46}NO_3$ $[M + H]^+$ 384.3472, found 384.3474.

Acknowledgements

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