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Graphical Abstract

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B. Suresh, A. Sravanth Kumar, P. Srihari and J. S. Yadav

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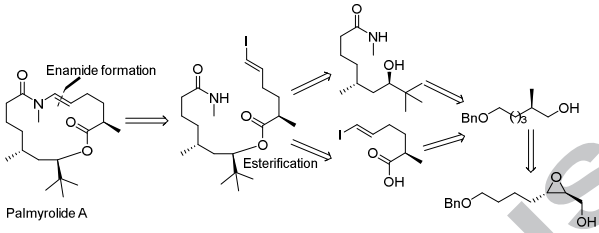

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Stereoselective total synthesis of palmyrolide A via intramolecular trans *N*-methyl enamide formation

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ABSTRACT

The stereoselective total synthesis of palmyrolide A was accomplished through macrocyclization reaction involving trans enamide formation by coupling of vinyl iodide with secondary amide in an intramolecular fashion. The two coupling partners, vinyl iodide **4** and secondary amide **3** were synthesized from the same intermediate alcohol **5**. Yamaguchi esterification and CBS-reduction are the other key steps involved in the synthesis.

Secondary metabolites produced by cyanobacteria attract significant attention due to their interesting biological properties like antitumor, antiviral, antibiotic, antimalarial, CNS and immunosuppressive activities.[1,2] The screening efforts from Gerwick *et al* had resulted in isolation and identification of the 15-membered macrocycle palmyrolide A as a potent neuroactive compound from two genera Leptolyngbya cf and Oscillatoria species.[3] This compound was also found to display sodium channel blocking activity in neuro-2a cell (IC_{50} = 5.2 μM) and functioned as VGSC antagonist to block veratridine-induced sodium influx.[4] The absolute structure of palmyrolide A with a rare *N*-methyl enamide and an intriguing t-butyl branch was confirmed only after its total synthesis.[5a]

Intrigued by the structural and biological properties displayed by enamide containing natural products,[6] we became interested in this class of compounds[7] and have targeted neuroactive palmyrolide A for the total synthesis. Of the five earlier contributions for palmyrolide A, Maio *et al*[5a,b] and Srinivas Reddy *et al*[5c] have used primary amide as the precursor for enamide formation and later methylated (*N*-methlyation) the enamide. Brimble and co-workers[5d] have reported the total synthesis involving the sequential ring closing metathesis/olefin isomerization reaction. Sudhakar et al[5e] have utilized an intramolecular dehydrative cyclization to form the *trans*-enamide. We have recently reported an improved procedure for the coupling of vinyl iodide and primary amide to generate an enamide macrocycle in an intramolecular fashion and utilized the methodology for the synthesis of several large ring macrocycles including palmyrolide A.[8] The procedure has now been extended to the coupling reaction of vinyl iodide with secondary amide to generate the corresponding *N*-substituted enamide and utilized for the total synthesis of palmyrolide A. The results pertaining to these investigations are presented herein.

Retrosynthesis

To begin with, our retrosynthetic analysis for palmyrolide A (Scheme **1**) revealed two key fragments **3** and **4** which can be coupled together in a convergent fashion initially through a Yamaguchi esterification reaction to result in an ester **2** and later subjected to an intramolecular coupling reaction between vinyl iodide and secondary amide resulting in the formation of the target molecule **1**. The key intermediates **3** and **4** can be synthesized following a divergent approach from the common intermediate **5**, which in turn can be easily accessible from chiral epoxy alcohol **6** in four steps. The chiral epoxy alcohol can be easily synthesized from commercially available inexpensive 1, 5-pentanediol.

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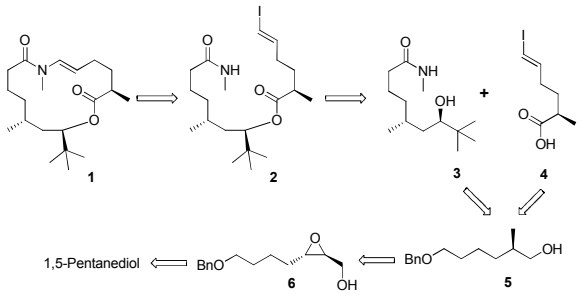
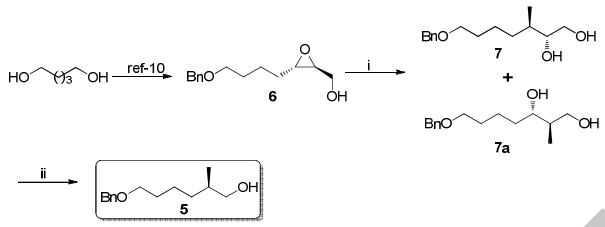


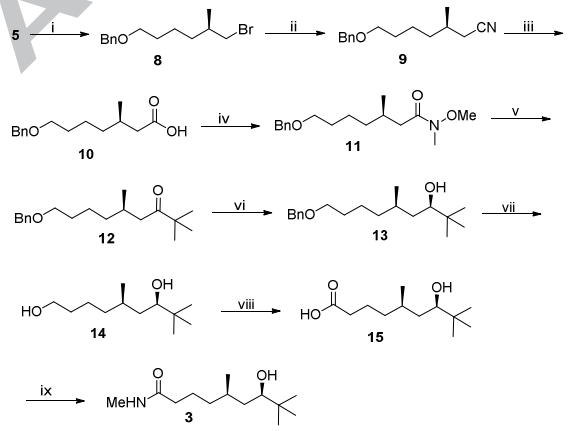
Scheme 1. Retrosynthesis of palmyrolide A

Our synthesis for the common intermediate **5** commenced with a ring opening reaction[9] of epoxide **6** that was synthesized in four steps following literature procedures starting from 1,5-pentanediol[10] to provide the mixture of **7** and **7a** in 93% yield. The mixture of diols was directly treated with $NaIO_4$ and the resulting crude aldehyde was further reduced with $NaBH_4$ to yield alcohol **5** along with easily separable unreacted **7a** (Scheme 2).



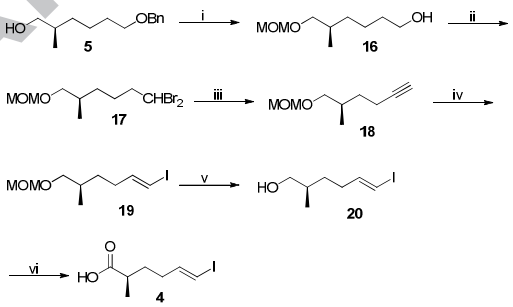
Scheme 2. Reagents and conditions: (i) Me_3Al, Hexanes, 0 ^oC, 1 h, 83%; (ii) (a) $NaIO_4$, THF:H_2O (3:1), 0 ^oC- rt, 1h; (b) $NaBH_4$, THF, rt, 0.5 h, 72% (for 2 steps)

Alcohol **5** was treated with triphenylphosphine (TPP) and carbon tetrabromide (CBr_4) to yield the corresponding bromide **8** and subjected to nucleophilic displacement reaction with NaCN to furnish the nitrile **9**. Compound **9** was converted to acid in two-step procedure and then coupled with Weinreb salt to provide Weinreb amide **11** (Scheme **3**) which upon treatment with ^tBuLi in diethyl ether at -78 ^oC provided the corresponding tert-butyl ketone **12** in 79% yield. Stereoselective reduction of ketone **12** with (*S*)-CBS[11] catalyst furnished the desired chiral alcohol **13** in 90% yield with 97% *de*. Compound **13** on debenzylation with Pd-C (10%) followed by oxidation of the resulting primary alcohol **14** with TEMPO and [bis(acetoxy)-iodo]benzene (BAIB) afforded the acid **15**, which was activated by ethyl chloroformate in presence of triethylamine and then treated with aq. 20% $MeNH_2$ to furnish the key fragment *N*-methyl amide[7a] **3** in 98% yield (Scheme 3)



Scheme 3. Reagents and conditions: (i) PPh_3, CBr_4, CH_2Cl_2, 0 ^oC- rt, 6h, 95%; (ii) NaCN, DMSO, 120 ^oC, 3 h, 92%; (iii) (a) DIBAL-H, CH_2Cl_2, -78 ^oC, 0.5 h; (b) $NaClO_2$, $NaH_2PO_4.H_2O$, 2-methyl-2-butene, t-BuOH:H_2O (3:1), 0 ^oC-rt, 8 h, 84% (for 2 steps); (iv) CDI, NMeHOMe.HCl, CH_2Cl_2, 0 ^oC-rt, 8 h, 91%; (v) t-BuLi, Diethyl ether, -78 ^oC, 0.5 h, 79%; (vi) (*S*)-CBS 1.0 M in toluene, BH_3.DMS, toluene, 0 ^oC-rt, 8 h, 90%, 97.3% de; (vii) H_2, Pd-C (10%), MeOH, 8 h, 98%; (viii) TEMPO, BAIB, acetonitrile, rt, 8 h, 94%; (ix) Ethyl chloroformate, Et_3N, 20% $MeNH_2$ in H_2O, CH_2Cl_2, 0 ^oC-rt, 0.5 h, 98%.

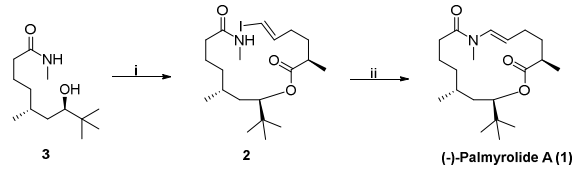
The alcohol **5** obtained in good quantities was also utilized for the synthesis of second key fragment **4** (Scheme **4**). Accordingly, alcohol **5** was initially protected as the corresponding MOM ether and subjected to debenzylation with Pd-C (10%) to yield the alcohol **16** in quantitative yield. **16** on oxidation with IBX followed by treatment with bromine in presence of triphenyl phosphite provided the *gem*-dibromide **17**. Elimination reaction occurred smoothly with an exposure of **17** to t-BuOK in the presence of 18-crown-6 to provide the alkyne **18**.[12] The terminal free acetylene **18** was converted to trans-vinyl iodide following Negishi's protocol[13] employing Schwartz reagent (generated in situ from zirconocene dichloride and DIBAL-H) followed by iodination with NIS to furnish **19** in 81% yield. MOM deprotection followed by oxidation of the resulting primary alcohol **20** provided the key acid fragment **4** with a vinyl iodide moiety (Scheme 4).



Scheme 4. Reagents and conditions: (i) (a) MOM-Cl, DIPEA, CH_2Cl_2, 0 ^oC-rt, 8 h, 98%; (b) H_2, Pd-C (10%), MeOH, 8 h, 95%; (ii) (a) IBX, DMSO, CH_2Cl_2, rt, 1 h; (b) $P(OPh)_3$, Br_2, TEA, CH_2Cl_2, -78 ^oC, 1 h, 90% (for 2 steps); (iii) t-BuOK, 18-crown-6, Hexanes, reflux, 8 h, 95%; (iv) Cp_2ZrCl_2, DIBAL-H, NIS, CH_2Cl_2, 50 ^oC, 1 h, 75%; (v) Dioxane.HCl 4M, THF, rt, 6 h, 90%; (vi) (a) IBX, DMSO, CH_2Cl_2, rt, 1 h; (b) $NaClO_2$, $NaH_2PO_4.H_2O$, 2-methyl-2-butene, t-BuOH:H_2O (3:1), 0 ^oC-rt, 8 h, 88% (for 2 steps)

With the two key fragments **3** and **4** in hand, the stage was set to proceed further for the target synthesis. As planned earlier, the final step for target synthesis would be a secondary enamide formation reaction. Thus, we proceeded initially with the coupling of two fragments **3** and **4** following Yamaguchi's protocol[14] to yield the ester **2** in 81% yield (Scheme 5). Although the coupling reaction of vinyl iodide with primary amide to get the corresponding enamide in an intramolecular fashion is well reported,[15,5a] to the best of our knowledge the same with secondary amide in an intramolecular fashion is not reported. It was also observed that the resulting primary enamides synthesized were existing in rotameric forms and sometimes tend to isomerize to get *cis* and *trans* isomers and hence have to be protected/*N*-methylated to get the stable products. This feature has made us to focus on *N*-methylated enamide formation reaction directly through the coupling of vinyl iodide with *N*-

methyl amide. Our initial attempts for intramolecular coupling reaction for enamide formation with substrate **2** following Buchwald's condition using CuI as catalyst, Cs_2CO_3 as base, *N, N*-dimethylethylenediamine as ligand and THF as solvent ended up with recovery of starting material. However, from our recent procedure with an improvement in selectivity and yield for the coupling reaction of vinyl iodide with primary amide,[8] we planned to investigate the same with secondary amide, since this would end up with the *N*-methylated enamide directly. We were delighted to note that the reaction was successful and resulted in the synthesis of target compound palmyrolide A **1** in 51% yield (69%, based on recovery of starting material) (Scheme 5). This reaction also becomes the first procedure[16] for an intramolecular coupling of trans-vinyl iodide with the secondary amide to generate *N*-methyl *trans* enamide. The spectroscopic data[17] of our synthetic compound was found to be identical with those of the reported natural product[3] and synthetic product.[5]



Scheme 5. Reagents and conditions: (i) **4**, 2, 4, 6-trichloro benzoyl chloride, DIPEA, THF, DMAP, toluene, 18 h, 81%, (ii) CuI (0.5 eq), CsF, *trans*-1, 2-diamino cyclohexane, toluene, 90 ^{o}C, 36 h, 51%.

To further check the scope of the optimized procedure for generating secondary enamide large ring macrocycles, we further investigated substrates with α, ω-vinyl iodide and secondary amide functionality having variable chain length (Entry 1,2,4,5 & 6, Table 1) and aromatic moiety (Entry 3, and 7, Table 1) within the chain to provide the corresponding coupled enamide macrolides. The methodology was also successfully utilized for the synthesis of an analogue compound desmethyl palmyrolide A (**4b**, Table 1).

In conclusion, we report a procedure for an intramolecular coupling of trans-vinyl iodide with secondary amide to provide the corresponding *N*-methyl trans enamide. This procedure was successfully utilized for the synthesis of a secondary enamide motif that ended up in the accomplishment of the total synthesis of palmyrolide A along with several other variable ring size macrocycles and an analogue compound desmethyl palmyrolide A. Application of this methodology for the synthesis of other natural products with *N*-methyl enamide motif is being currently pursued in the laboratory.

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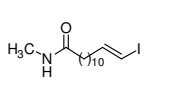
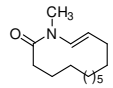
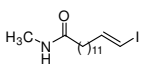
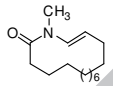
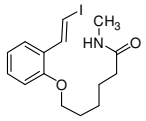
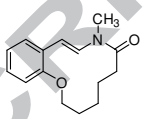
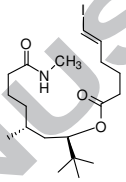
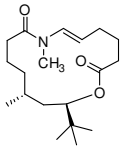
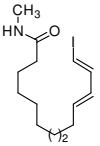
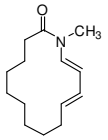
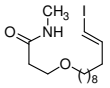
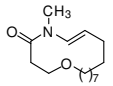
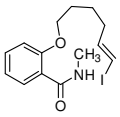
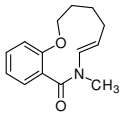
Table 1. Examples for intramolecular *N*-methyl-trans enamide formation.

Entry	Substrate	Product[a]	Yield
1	 **1a**	 **1b**	50%
2	 **2a**	 **2b**	48%
3	 **3a**	 **3b**	68%
4	 **4a**	 **4b**	51%
5	 **5a**	 **5b**	55%
6	 **6a**	 **6b**	54%
7	 **7a**	 **7b**	60%

[a]The reaction was performed in toluene at 90 ^{o}C with CsF(2 eq), CuI (0.7 eq) and (+/-)-1, 2-diamino cyclohexane (0.7 eq).

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:.

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(16) Optimized procedure for intramolecular coupling reaction of vinyl iodide with secondary amide. The mixture of substrate (0.065 mmol) and cesium fluoride (0.13 mmol) in dry toluene (4 mL) were taken in an oven dried sealed tube fitted with septum and was purged with argon gas for 10 min. Then copper iodide (0.045 mmol) and (±)-1, 2 diaminocyclohexane (0.045 mmol) were added sequentially to the reaction mixture and purging was continued for further 10 min. The reaction mixture was then stirred vigorously at 90 °C for 36 h. The reaction was allowed to cool to room temperature and diluted with EtOAc, filtered through a short pad of silica gel, washed with EtOAc and the filtrate was concentrated in vacuum. Purification by flash column chromatography affords the corresponding enamide macrocycle.

(17) Spectroscopic data for **3**. $[\alpha]_D^{20}$ = + 32.6 (*c* 0.85, $CHCl_3$); IR (neat) 3306, 2953, 2869, 1652, 1560, 769 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.60 (bs, 1H), 3.28 (dd, *J* = 10.2 Hz, *J* = 1.9 Hz, 1H), 2.81 (d, *J* = 4.9 Hz, 3H), 2.17 (t, *J* = 8.3 Hz, 2H), 1.79-1.46 (m, 4H), 1.40-1.32 (m, 1H), 1.27-1.17 (m, 1H), 1.12-1.02 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.0, 77.2, 39.0, 36.5, 34.9, 34.5, 29.3, 26.3, 25.7 (3C), 23.1, 20.9; HRMS (ESI) *m/z* calculated for $C_{13}H_{27}O_2NNa$ $[M + Na]^+$: 252.19340, found 252.19245. **4**. $[\alpha]_D^{20}$ = - 16.8 (*c* 1.0, $CHCl_3$); IR (neat) 3063, 3031, 2933, 2861, 1707, 1455, 1100, 772, 736, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 6.52-6.46 (m, 1H), 6.06 (td, *J* = 14.3 Hz, *J* = 1.4 Hz, 1H), 2.49 (sextet, *J* = 6.9 Hz, 1H), 2.12 (dq, *J* = 7.6 Hz, *J* = 1.2 Hz, 2H), 1.78-1.77 (m, 1H), 1.61–1.50 (m, 1H), 1.19 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): *δ* 182.7, 145.2, 75.6, 38.5, 33.5, 31.8, 16.8; HRMS (ESI): *m/z* calculated for $C_7H_{11}IO_2$ $[M]^+$ 253.98037, found 253.98119. **2**. $[\alpha]_D^{20}$ = + 14.78 (*c* 1.05, $CHCl_3$); IR (neat) 3301, 3090, 2959, 1727, 1648, 1555, 1461, 1369, 1163, 1064, 959 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.51 (dt, *J* = 14.3 Hz, *J* = 6.8 Hz, 1H), 6.04 (d, *J* =14.3 Hz, 1H), 5.96 (bs, 1H), 4.82-4.73 (m, 1H), 2.82 (d, *J* = 5.3 Hz, 3H), 2.53-2.40 (m, 1H), 2.24-2.01 (m, 4H), 1.90-1.70 (m, 3H), 1.57-1.34 (m, 5H), 1.17 (d, *J* = 6.8 Hz, 3H), 1.08-0.96 (m, 1H), 0.94-0.83 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.4, 173.9, 145.4, 79.0, 75.3, 39.3, 37.6, 36.2, 34.6 (2C), 33.7, 32.1, 29.0, 26.2, 26.0 (3C), 22.9, 20.9, 17.4; HRMS (ESI) *m/z* calculated for $C_{20}H_{36}O_3NINa$ $[M + Na]^+$: 488.16321, found 488.16031. **1**. $[\alpha]_D^{20}$ = - 21.50 (*c* 0.2, $CHCl_3$); IR (neat) 3445, 2959, 2928, 2871, 1725, 1675, 1646, 1463, 1126 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 6.47 (d, *J* = 13.9 Hz, 1H), 5.28 (dt, *J* = 14.0 Hz, *J* = 7.0 Hz, 1H), 4.89 (dd, *J* = 11.0 Hz, *J* = 1.4 Hz, 1H), 3.05 (s, 3H), 2.50-2.44 (m, 1H), 2.43-2.34 (m, 2H), 2.33-2.26 (m, 2H), 1.84-1.73 (m, 3H), 1.70-1.51 (m, 2H), 1.51-1.44 (m, 1H), 1.39 (ddd, *J* = 14.3 Hz, *J* = 8.7 Hz, *J* =1.9 Hz, 1H), 1.37-1.31 (m, 1H), 1.21 (d, *J* = 7.2 Hz, 3H), 1.09-1.03 (m, 1H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.87 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 175.3, 172.9, 130.6, 117.3, 77.0, 38.9, 35.7, 35.3, 34.6, 34.5, 32.8, 31.7, 29.3, 27.0, 26.1 (3C), 24.3, 20.6, 16.8; HRMS (ESI): *m/z* calculated for $C_{20}H_{35}O_3NNa$ $[M + Na]^+$ 360.25092, found 360.24971.

Highlights

- Intramolecular coupling of vinyl iodide with secondary amide is achieved for the first time.
- Large ring size macrolides with trans enamide functionality are synthesized.
- This method is very much useful for generating trans enamides exclusively.