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Asymmetric Total Synthesis and Absolute Stereochemistry of the Neuroactive Marine Macrolide Palmyrolide A

Rodolfo Tello-Aburto, Emily M. Johnson, Cheyenne K. Valdez, and William A. Maio*

Department of Chemistry and Biochemistry, New Mexico State University, Las Cruces, New Mexico 88003, United States

wmaio@nmsu.edu

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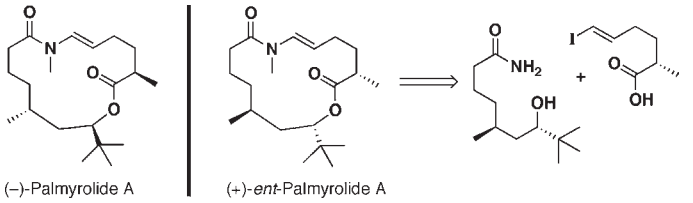
ABSTRACT



The first asymmetric total synthesis and determination of the absolute configuration for the neuroactive marine macrolide palmyrolide A is described. The highlight of the synthesis is macrocyclization *via trans*-enamide formation catalyzed by copper(I) iodide and cesium carbonate. Comparison with the authentic spectral data confirms the synthesis of (+)-*ent*-palmyrolide A.

The study of marine organisms continues to provide natural products with intricate molecular architecture, unique biological activity, and great potential for use as modern chemotherapeutics. Recently, Gerwick and coworkers reported the isolation and structural elucidation of palmyrolide A (**1**), a neuroactive macrolide from a cyanobacterial assemblage comprised of *Leptolyngbya* and *Oscillatoria* species collected at Palmyra Atoll, south of Hawaii.[1] Initial biological studies revealed **1** to be a potent inhibitor of calcium ion oscillations in murine cerebrocortical neurons and to possess sodium ion channel blocking ability in neuroblastoma cells.[1] When screened against human lung adenocarcinoma cells, the authors note no appreciable cytotoxicity.[1]

The overall connectivity of (−)-palmyrolide A was determined by detailed NMR studies.[1] However, due to the resistance of the lactone to hydrolyze under a variety of reaction conditions, the authors were unable to degrade the macrolide into acyclic fragments that would prove useful in determining the absolute stereochemistry.[1] As a result, the authors performed the Murata *J*-based configurational analysis[2] on the macrocycle itself to determine the relative stereochemistry between the C(5) methyl and the C(7) *tert*-butyl centers. These data, in conjunction with NOE correlations, suggested the relationship between C(5) and C(7) was *syn*.[1]

We became interested in (−)-palmyrolide A as a synthetic target not only because of its interesting biological profile but also due to the presence of two unique structural elements: the rare *tert*-butyl moiety and the *trans*-*N*-methyl enamide. A search of the literature reveals few examples of isolated natural products that contain a sterically encumbered *tert*-butyl group α to the lactone ester,[3] with (−)-apratoxin A being the sole example confirmed by total synthesis.[4] It should be noted that, for apratoxin, the relative stereochemistry between its C(37) methyl and C(39) *tert*-butyl is *anti*.[5] In the case of palmyrolide A, Gerwick speculates that the *tert*-butyl structural

(1) Pereira, A. R.; Cao, Z.; Engene, N.; Soria-Mercado, I. E.; Murray, T. F.; Gerwick, W. H. *Org. Lett.* **2010**, *12*, 4490–4493.

(2) (a) Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866–876. (b) This method was successfully applied to the structure elucidation of the (−)-apratoxin A macrolide. See ref 3a.

(3) (a) Luesch, H.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J.; Corbett, T. H. *J. Am. Chem. Soc.* **2001**, *123*, 5418–5423. (b) Klein, D.; Braekman, J. C.; Daloze, D.; Hoffmann, L.; Castillo, G.; Demoulin, V. *J. Nat. Prod.* **1999**, *62*, 934–936. (c) Matthew, S.; Salvador, L. A.; Schupp, P. J.; Paul, V. J.; Luesch, H. *J. Nat. Prod.* **2010**, *73*, 1544–1552.

(4) For the most recent total synthesis, see: Numajiri, Y.; Takahashi, T.; Doi, T. *Chem.—Asian J.* **2009**, *4*, 111–125. For the first total synthesis, see: Chen, J.; Forsyth, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 8734–8735.

(5) For the apratoxin numbering convention, see ref 3a.

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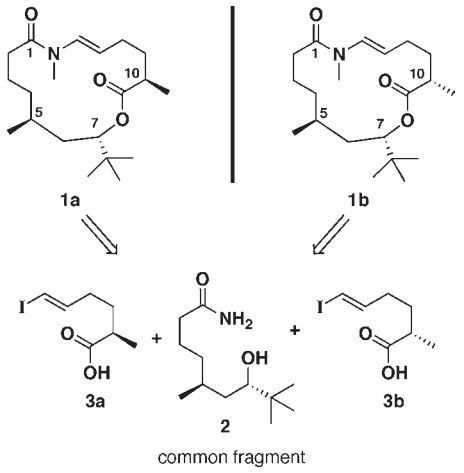
Scheme 1. Retrosynthetic Analysis



unit may be evolutionary, developed as a way to prevent hydrolysis of the bioactive lactone moiety under natural conditions.[1]

N-Methyl enamide macrocycles are exceedingly rare in the natural product literature, with few reported examples;[3b,c] none have been confirmed by total synthesis. Interestingly, these compounds all contain a *tert*-butyl group α to the lactone ester within their molecular framework and are likely derived from the same genus of cyanobacteria.[1] A related family of macrolides contains an *N*-H enamide,[6] although with *cis* olefin geometry. Several other compounds have side chains decorated with *N*-H enamides;[7] however to the best of our knowledge, there is only one that features an *N*-methyl enamide subunit.[7f]

Due to uncertainty regarding the absolute configuration of palmyrolide A,[1] at the outset of our synthetic campaign we decided to target all possible diastereomeric combinations. While Gerwick identified the relative configuration between the C(5) methyl and the C(7) *tert*-butyl to be *syn*,[1] based on the apratoxin A literature,[3a,4] we believed that the relationship between these two groups could also be *anti*. In order to most efficiently address the unknown absolute stereochemistry, we decided to exploit a synthetic route that would allow us to synthesize all diastereomers concurrently. Herein, we report our work on the C(5)−C(7) *anti* series.

In the isolation report, the absolute stereochemistry of the C(10) methyl group was unequivocally assigned to be in the *R* configuration.[1] Rather than design our synthetic plan around the known C(10) center, we thought that a more economical approach would be to target only one of the two possible C(5)−C(7) *anti* combinations and then vary the stereochemistry at C(10). In this way, we would utilize a common fragment (*cf.* **2**) to gain access to both *anti* diastereomeric combinations of palmyrolide A (**1a** and **1b**, Scheme 1) representing one compound from each enantiomeric set. We chose the C(5)-*S*, C(7)-*S* arrangement, based on guidance from Gerwick,[8] to coincide with the absolute stereochemistry found in apratoxin A.[3a]

Retrosynthetically, we believed that macrocyclization exploiting a method to unite a primary amide with a vinyl iodide would prove facile.[9,10] A related macrocyclization has been documented;[9j] however to the best of our knowledge, there has been no use of this strategy for the construction of a 15-membered macrocycle, or for the formation of a *trans* enamide. Further simplification reveals amide alcohol **2**, which is common to both targets, and vinyl iodides **3a** and **3b** (Scheme 1). These fragments could be combined in the forward direction under mild reaction conditions *via* formation of a mixed anhydride.

To establish the key *anti*-stereorelationship between C(5) and C(7), we relied on elegant chemistry developed by Cavelier and co-workers during their recent synthesis of oxoapratoxin,[11] an oxazoline analogue of apratoxin A. The synthesis of fragment **2** commenced with a D-proline catalyzed asymmetric aldol union between pivaldehyde and acetone to furnish β-hydroxy ketone (−)-**4**, following the known literature account[11] (Scheme 2). In the Cavelier studies, stereoselective *syn*-reduction of (−)-**4** was affected using diethylmethoxyborane/$NaBH_4$,[12] which provided an acceptable mixture of *syn* and *anti* diastereomers (95:5).

(6) (a) For a review article showcasing several examples, see: Gournelis, D. C.; Laskaris, G. G.; Verpoorte, R. *Nat. Prod. Rep.* **1997**, *14*, 75–82. (b) See also: Lin, H.-Y.; Chen, C.-H.; You, B.-J.; Liu, K. C. S. C.; Lee, S.-S. *J. Nat. Prod.* **2000**, *63*, 1338–1343.

(7) For several examples, see: (a) Erickson, K. L.; Beutler, J. A.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188–8192. (b) Galinis, D. L.; McKee, T. C.; Pannell, L. K.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8968–8969. (c) McKee, T. C.; Galinis, D. L.; Pannell, L. K.; Cardellina, J. H., II; Laakso, J.; Ireland, C. M.; Murray, L.; Capon, R. J.; Boyd, M. R. *J. Org. Chem.* **1998**, *63*, 7805–7810. (d) Kim, J. W.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Org. Chem.* **1999**, *64*, 153–155. (e) Kohno, J.; Koguchi, Y.; Nishio, M.; Nakao, K.; Kuroda, M.; Shimizu, R.; Ohnuki, T.; Komatsubara, S. *J. Org. Chem.* **2000**, *65*, 990–995. (f) Nogle, L. M.; Gerwick, W. H. *Org. Lett.* **2002**, *4*, 1095–1098.

(8) Personal communication, 2011.

(9) For copper-catalyzed vinyl halide/amide unions, see: (a) Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* **1991**, 1443–1446. (b) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333–1336. (c) Shen, R.; Lin, C. T.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 5650–5651. (d) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667–3669. (e) Nakamura, R.; Tanino, K.; Miyashita, M. *Org. Lett.* **2003**, *5*, 3583–3586. (f) Han, C.; Shen, R.; Su, S.; Porco, J. A., Jr. *Org. Lett.* **2004**, *6*, 27–30. (g) Coleman, R. S.; Liu, P.-H. *Org. Lett.* **2004**, *6*, 577–580. (h) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809–1812. (i) Shen, R.; Inoue, T.; Forgac, M.; Proco, J. A., Jr. *J. Org. Chem.* **2005**, *70*, 3686–3692. (j) Toumi, M.; County, F.; Evano, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 572–575. (k) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054–3131.

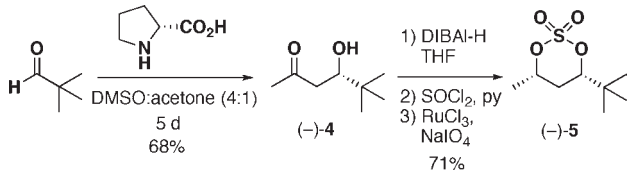
(10) For a good review of the enamide literature pre-2000, see ref 10b and references cited therein. For select methods post-2000, see: (a) Fürstner, A.; Brehm, C.; Cancho-Grande, Y. *Org. Lett.* **2001**, *3*, 3955–3957. (b) Wallace, D. J.; Klauber, D. J.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749–4752. (c) Brice, J. L.; Meerdink, J. E.; Stahl, S. S. *Org. Lett.* **2004**, *6*, 1845–1848. (d) Yudha, S. S.; Kuninobu, Y.; Takai, K. *Org. Lett.* **2007**, *9*, 5609–5611. (e) Bolshan, Y.; Batey, R. A. *Angew. Chem.* **2008**, *120*, 2139–2142. (f) Arndt, M.; Salih, K. S.M.; Fromm, A.; Goossen, L. J.; Menges, F.; Niedner-Schatteburg, G. *J. Am. Chem. Soc.* **2011**, *133*, 7428–7449. (g) Nicolaou, K. C.; Jiang, X.; Lindsay-Scott, P. J.; Corbu, A.; Yamashiro, S.; Bacconi, A.; Fowler, V. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 1139–1144.

(11) Gilles, A.; Martinez, J.; Cavelier, F. *J. Org. Chem.* **2009**, *74*, 4298–4304.

(12) Chen, K. M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923–1926.

Unfortunately, in our hands this reduction strategy did not yield a synthetically workable mixture of isomers. Chromatographic separation also proved difficult. Pleasingly, recourse to a stereoselective reduction using 2.5 equiv of DIBAl-H[13] provided the requisite diol in excellent yield and high diastereoselectivity (Scheme 2). This modification also obviated the need for a challenging silica gel purification step. Next, in two synthetic operations involving (1) treatment with thionyl chloride in pyridine and (2) oxidation using RuO_4, the *syn*-diol was easily converted into cyclic sulfate (−)-**5** in good overall yield.[14]

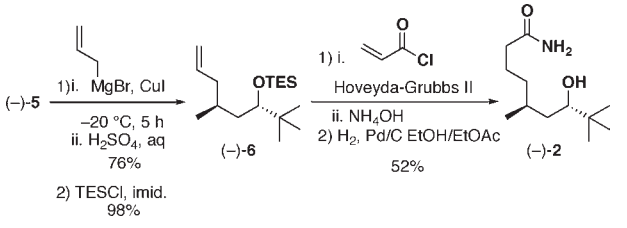
Scheme 2. Synthesis of Cyclic Sulfate **5**



Nucleophilic ring opening of (−)-**5**[15] using a mixed organometallic species derived from allylmagnesium bromide and copper iodide, following the procedure of Cavelier,[11] and alcohol protection with TESCl provided alkene (−)-**6**, possessing the *anti*-C(5)-*S*, C(7)-*S* stereochemical arrangement we targeted (Scheme 3).[16] Of note, the triethylsilyl group in (−)-**6** is the only protecting group employed during our synthesis of palmyrolide A.

Union of (−)-**6** with freshly distilled acryloyl chloride[17a] employing the Hoveyda–Grubbs II precatalyst, followed by *in situ* addition of ammonium hydroxide, allowed access to the primary amide. The analogous cross metathesis using acrylamide and the Grubbs II precatalyst[17b] was also tried; however this process gave good but somewhat inferior results compared to acryloyl chloride (36% vs 58%, respectively). In the next step, hydrogenation of the α,β-unsaturation occurred with concomitant loss of the labile triethylsilyl group[18] and provided fragment (−)-**2** in good overall yield (Scheme 3).

Scheme 3. Synthesis of Fragment **2**



(13) Kiyooka, S.-i.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3009–3012.

(14) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538–7539. Also see ref 11.

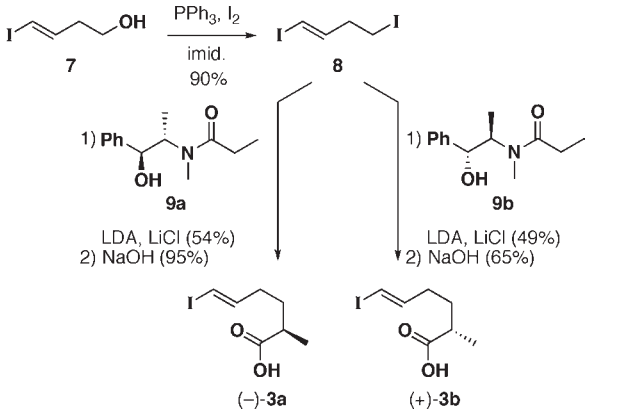
(15) For a review article documenting the reactivity of cyclic sulfates, see: Byun, H.-S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051–7091.

(16) Silyl ether (−)-**6** is a known compound. See ref 11.

It should be noted that during the cross metathesis step, trace HCl from the acryloyl chloride is sufficient to cleave some of the silyl ether protecting group. As a result, the balance in chemical yield is a byproduct arising from free alcohol esterification with acryloyl chloride. Unfortunately, attempts to hydrolyze the ester were met with no success. We believe this is due to the steric constraints of the neighboring *tert*-butyl group preventing nucleophilic attack on the ester carbonyl. This result is consistent with the reported unsuccessful attempts to hydrolyze the lactone of palmyrolide A.[1]

With amide alcohol **2** in hand, we turned our attention to the fabrication of vinyl iodides **3a** and **3b**. The syntheses of these fragments began employing known alcohol **7**, produced in three literature operations from commercially available 3-butyn-1-ol.[19] Alcohol to iodide interconversion proceeded in high yield, and the resultant diiodide (**8**) was used in the Myers alkylation[20] with (*S,S*)-propionamide **9a** and separately with (*R,R*)-propionamide **9b** (Scheme 4). Pleasingly, both alkylations proceeded in good yield and in high diastereoselectivity (>20:1 by ^1H NMR). These yields are consistent with the Myers studies which noted limited reactivity with substrates bearing β-alkyl branching or alkoxy groups.[20] We believe the presence of the β-vinyl iodide of **8** may be responsible for the diminished yields we observed relative to unhindered literature examples.[20] Subsequent hydrolysis with NaOH provides acids (−)-**3a** and (+)-**3b**,[21] with negligible loss of stereopurity, and complete preservation of the *trans* vinyl iodide unit.[22]

Scheme 4. Assembly of Vinyl Iodides **3a** and **3b**



(17) (a) Ferrié, L.; Bouzbouz, S.; Cossy, J. *Org. Lett.* **2009**, *11*, 5446–5448. (b) Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277–1279.

(18) Sajiki, H.; Ikawa, T.; Hattori, K.; Hirota, K. *Chem. Commun.* **2003**, 654–655.

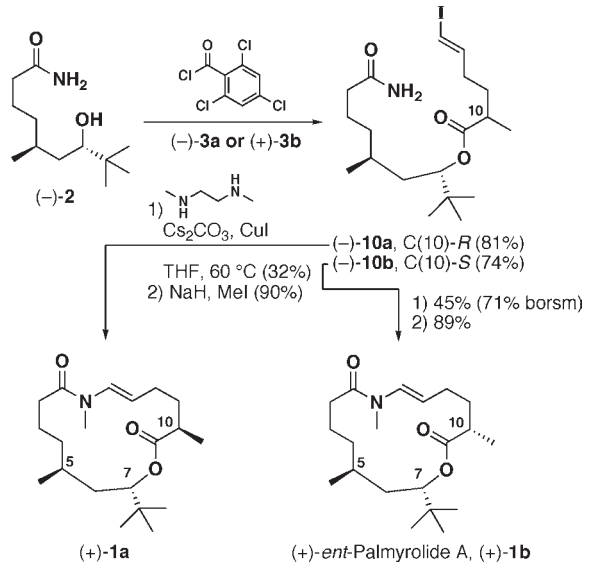
(19) (a) Munakata, R.; Ueki, T.; Katakai, H.; Takau, K.; Tadano, K.-i. *Org. Lett.* **2002**, *3*, 3029–3033. (b) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778–17788. (c) Alcohol **7** can also be prepared in one synthetic step from 3-butyn-1-ol. See: Huang, Z.; Negishi, E.-i. *Org. Lett.* **2006**, *8*, 3675–3678.

(20) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.

(21) The yield of (+)-**3b** is unoptimized.

(22) Elimination of *Z*-vinyl iodides readily occurs upon treatment with NaOMe. For example, see ref 19a.

Scheme 5. Synthesis of Macrocycles **1a** and **1b**



Union of the common amide alcohol fragment (**2**) with either (−)-**3a** or (+)-**3b**, exploiting 2,4,6-trichlorobenzoyl chloride as a coupling agent,[23] allowed access to macrocyclization precursors (−)-**10a** and (−)-**10b**, respectively (Scheme 5). Formation of the 15-membered ring, using a high-dilution modification (0.01 M) to the copper(I) iodide/cesium carbonate conditions developed by Buchwald,[9d] afforded the *trans*-*N*-H enamide macrocycles in modest yield. To the best of our knowledge, this is the first use of the copper-promoted reaction conditions for the formation of *trans*-enamide macrocycles. In the final step, treatment of each macrocycle separately with sodium hydride followed by iodomethane[24] provided the requisite *trans*-*N*-methyl enamides (+)-**1a** and (+)-**1b** (Scheme 5) in excellent yield.

At this stage, a comparison with the reported spectra of palmyrolide A[1] was made. Compound (+)-**1a**, featuring the natural C(10)-*R* stereochemistry, did not match the literature values reported by Gerwick. Pleasingly, there was a complete ^{1}H and ^{13}C NMR match with macrolide (+)-**1b**, where the C(10) methyl group is inverted relative to the natural macrolide. Optical rotation comparison confirms that we have synthesized the enantiomer of (−)-palmyrolide A, (+)-*ent*-palmyrolide A {$[\alpha]_D$ = +23 (*c* = 0.65, $CHCl_3$), lit. $[\alpha]_D$ = −29 (*c* = 0.9, $CHCl_3$)}.[1] The longest linear sequence is 11 steps from commercially available starting materials, or 6 steps from known silyl ether (−)-**6**. Importantly, we have confirmed that the stereochemical relationship between the C(5) methyl and the C(7) *tert*-butyl is *anti*, and not *syn*, as originally proposed in the isolation report.[1] Also of interest, the absolute stereochemistry at C(5) and C(7) found in (−)-palmyrolide A is opposite that found in apratoxin A.[3a]

A full account of this work, including syntheses of the complementary C(5) methyl, C(7) *tert*-butyl *syn* series, and the synthesis of natural (−)-palmyrolide A, will be reported in due course.

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Supporting Information Available. Detailed experimental procedures, as well as scans of ^{1}H and ^{13}C NMR spectra are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.