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Total Synthesis of the Initially Reported and Revised Structures of the Neuroprotective Agent Palmyrolide A

Andrew D. Wadsworth, Daniel P. Furkert, Jonathan Sperry, and Margaret A. Brimble*

School of Chemical Sciences, The University of Auckland, 23 Symonds Street, Auckland, 1010, New Zealand

m.brimble@auckland.ac.nz

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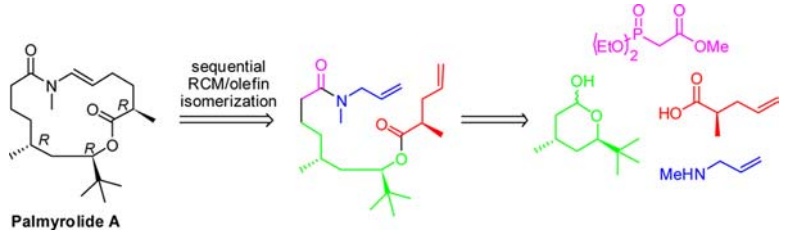
ABSTRACT



The total syntheses of the initially reported and revised structures of the neuroprotective agent palmyrolide A are reported. The key macrocyclization step was achieved using a sequential ring closing metathesis/olefin isomerization reaction. The synthetic work described herein serves to confirm the recent structural revision of this unusual natural product.

As part of a drug discovery and screening program, Gerwick and co-workers recently reported the isolation of palmyrolide A,[1] a neuroprotective macrolide with an uncommon *N*-methyl enamide moiety[2] from *Leptotyngbya cf. sp.* and *Oscillatoria sp.* (Figure 1). Murine cerebrocortical neurons treated with palmyrolide A showed a significant decrease in Ca^{2+} oscillations, along with promising neuroprotective properties.

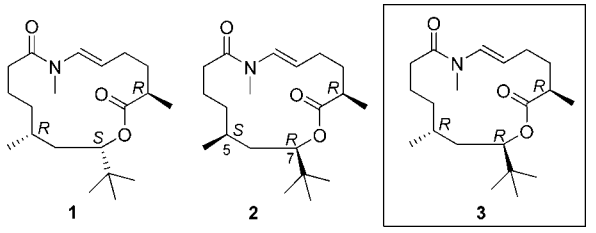


Figure 1. Initially proposed (**1**, **2**) and revised (**3**) structures of palmyrolide A.

These biological properties, combined with its low cytotoxicity, render palmyrolide A an excellent candidate for further pharmacological evaluation.[1]

Palmyrolide A was initially proposed to possess a *syn*-relationship between the stereocenters at C(5) and C(7), leading to the assignment of the natural product as either macrolide **1** or **2** (Figure 1).[1] However, this assignment has since been revised based on an elegant total synthesis by Maio and co-workers who established that the natural product actually possesses *anti*-configured C(5) and C(7) stereocenters (**3**; Figure 1).[3] Herein, we now report the asymmetric synthesis of **1**, *ent*-**2**, and the revised structure **3** of palmyrolide A, thereby further confirming the structural revision of the natural product.

At the outset of this project, the work of Maio[3] had not yet been reported and hence at this time our initial goal was to confirm the absolute configuration of the natural

(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) Natural *N*-methyl enamide macrocycles are rare: (a) Klein, D.; Braekman, J.; Daloze, D. *Tetrahedron Lett.* **1996**, *42*, 7519–7520. (b) Klein, D.; Braekman, J.; Daloze, D.; Hoffman, 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. (d) Soo Kang, H.-S.; Krunic, A.; Orjala, J. *Tetrahedron Lett.* **2012**, *53*, 3563–3567.

(3) (a) Tello-Aburto, R.; Johnson, E. M.; Valdez, C. K.; Maio, W. A. *Org. Lett.* **2012**, *14*, 2150–2153. (b) Tello-Aburto, R.; Newar, T. D.; Maio, W. A. *J. Org. Chem.* **2012**, *77*, 6271–6289.

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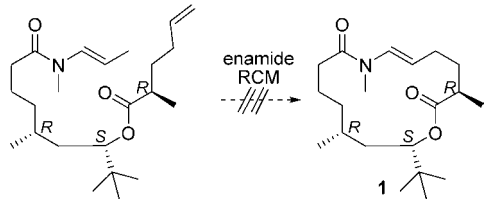
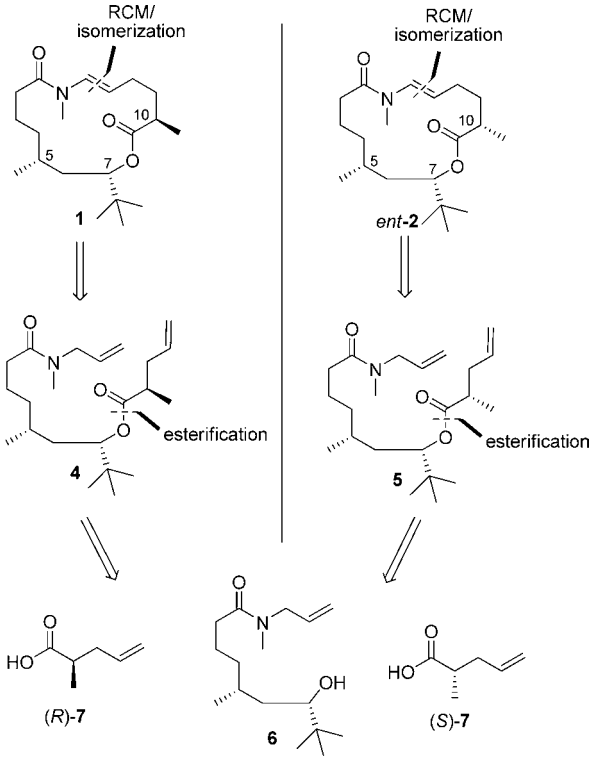
product by synthesizing the two C(5)−C(7) *syn*-configured macrolides **1** and *ent*-**2**.[1] Our original approach was to employ an enamide ring closing metathesis (RCM)[4] approach as the final, macrocyclization step in the synthesis of palmyrolide A (Scheme 1). Unfortunately, despite attempting a plethora of RCM conditions, no macrocyclization was ever observed (Scheme 1). Although the full details are not discussed herein, knowledge of this failed approach is necessary when considering the modified, ultimately successful syntheses detailed herein.

Scheme 1. Original Macrocyclization Approach



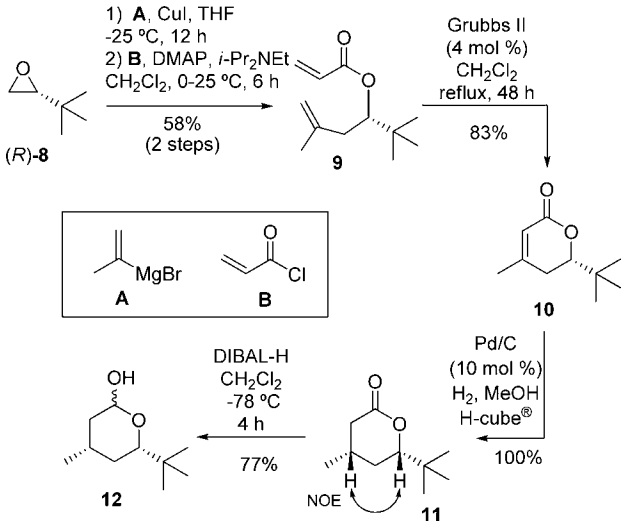
In a modified approach, it was envisioned the key macrocyclization step could be achieved using a sequential RCM/olefin isomerization sequence,[5] with the isomerization possibly occurring in tandem with RCM in the presence of the Grubbs' catalyst. The RCM precursors **4** and **5** would be constructed from the common intermediate alcohol **6** by esterification with carboxylic acids (*R*)-**7**[6a,b] or (*S*)-**7**,[6a,c] respectively (Scheme 2).

Scheme 2. Retrosynthetic Analysis



The synthesis of fragment **6** commenced with the copper promoted reaction of the known (*R*)-epoxide **8**[7] with isopropenylmagnesium bromide and subsequent esterification with acryloyl chloride to produce diene **9**. Smooth RCM gave dihydropyranone **10**, which upon hydrogenation gave lactone **11** as a single *syn*-diastereomer,

Scheme 3. Synthesis of Lactols **12**



as confirmed by NOE studies. Finally, straightforward reduction of lactone **11** provided **12** as a mixture of anomeric lactols (Scheme 3).

Lactols **12** were treated with the anion of phosphonate **13**, affording an enoate that was subjected to hydrogenation and hydrolysis (Scheme 4). The resulting carboxylic acid was then coupled with commercially available *N*-methylallylamine to afford the key alcohol **6**. Despite the hindered nature of alcohol **6**, use of the Yamaguchi conditions[8] enabled smooth esterification of **6** with (*R*)-**7** and (*S*)-**7**, affording **4** and **5** respectively, thus setting the stage for the key macrocyclization step (Scheme 4).

Complete consumption of diene **4** was observed after treatment with Grubbs' second generation catalyst for two days; however only RCM took place with no evidence that isomerization had occurred (Scheme 5). A separate isomerization step was therefore conducted

(4) (a) Toumi, M.; Rincheval, V.; Young, A.; Gergeres, D.; Turos, E.; Couty, F.; Mignotte, B.; Evano, G. *Eur. J. Org. Chem.* **2009**, 3368–3386. (b) Toumi, M.; Couty, F.; Evano, G. *J. Org. Chem.* **2008**, *73*, 1270–1281.

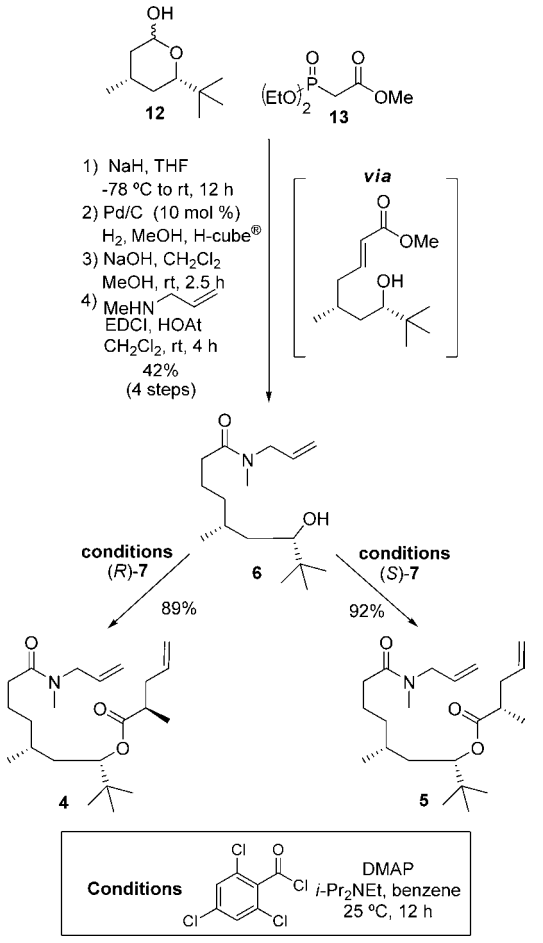
(5) Fustero, S.; Sánchez-Roselló, M.; Jiménez, D.; Sanz-Cervera, J. F.; del Pozo, C.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 2706–2714.

(6) (a) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511. (b) Zhang, K.; Peng, Q.; Hou, X. L.; Wu, Y. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1741–1744. (c) Fécourt, F.; Lopez, G.; Van Der Lee, A.; Martinez, J.; Dewynter, G. *Tetrahedron: Asymmetry* **2010**, *21*, 2361–2366.

(7) Nielsen, L. P. C.; Stevenson, C. P.; Blackmond, D. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 1360–1362. (b) Pouységu, L.; Chassaing, S.; Dejugnac, D.; Lamidy, L. M.; Miqueu, K.; Sotiropoulos, J. M.; Quideau, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 3552–3555.

(8) (a) Ma, D.; Zou, B.; Cai, G.; Hu, X.; Liu, J. O. *Chem.—Eur. J.* **2006**, *12*, 7615–7626. (b) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *7*, 1989–1993.

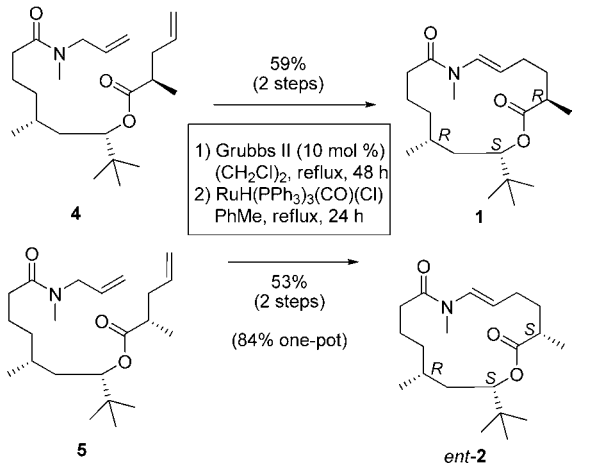
Scheme 4. Synthesis of RCM Precursors **4** and **5**



with carbonylchlorohydridotris(triphenylphosphine)-ruthenium(II)[9,10] in toluene under reflux for 24 h to afford macrocycle **1** in good yield over two steps. To the best of our knowledge, this reaction constitutes the first reported isomerization of an *N*-allylated tertiary amide in a macrocyclic setting.[11,12] Diene **5** was subjected to the same sequential RCM/isomerization conditions to afford *ent*-**2**, also in good yield (Scheme 5). This RCM/isomerization could also be conducted in one pot with excellent yield (84%), as exemplified by conversion of **5** to *ent*-**2** (Scheme 5).

Comparison of the ^{1}H and ^{13}C NMR data for synthetic **1** and *ent*-**2** with that of the natural product revealed several significant discrepancies, particularly the ^{1}H NMR chemical shifts for the olefinic protons. Coincidentally, it was at

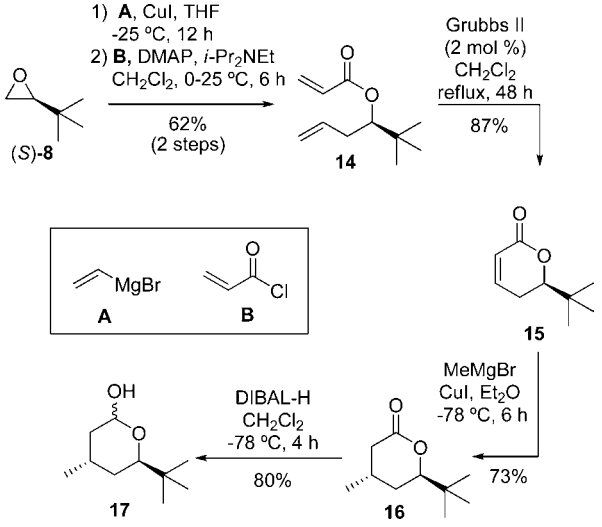
Scheme 5. Synthesis of Macrolides **1** and *ent*-**2**



this stage that the first total synthesis and structural revision of palmyrolide A[3] was reported, and as such, our own synthetic studies were therefore redirected toward the revised structure of the natural product (**3**). To achieve this goal, use of the *anti*-configured lactols **17** in our established synthetic sequence was required, the synthesis of which is detailed in Scheme 6.

Initial ring opening of epoxide (*S*)-**8** was effected using vinylmagnesium bromide followed by esterification to give diene **14**. Smooth RCM gave dihydropyranone **15** which upon addition of the cuprate derived from methylmagnesium bromide gave the *anti*-alkylated product **16** as a single diastereomer, the ^{1}H and ^{13}C NMR of which were identical to those of known *ent*-**16**.[13] Straightforward reduction of lactone **16** gave a mixture of lactols **17** (Scheme 6).

Scheme 6. Synthesis of Lactols **17**



(9) Levison, J. J.; Robinson, S. D. *Inorg. Phys. Theor.* **1970**, 2947–2954.

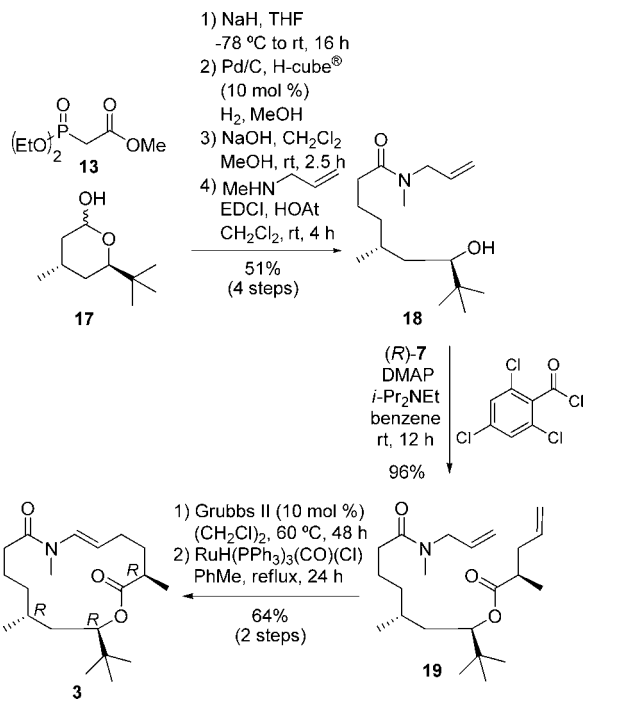
(10) Yue, C. J; Liu, Y.; He, R. *J. Mol. Catal. A* **2006**, *259*, 17–23.

(11) For the isomerization of a macrocyclic *N*-allylated secondary amide, see: Sergeyev, S. A.; Hesse, M. *Helv. Chim. Acta* **2003**, *86*, 465–473.

(12) For examples on acyclic substrates, see: (a) Murai, T.; Kasai, Y.; Ishihara, H.; Kato, S. *J. Org. Chem.* **1992**, *57*, 5542–5545. (b) Neugnot, B.; Cintrat, J.-C.; Rousseau, B. *Tetrahedron* **2004**, *60*, 3575–3579. (c) Krompiec, S.; Pigulla, M.; Kuźnik, N.; Krompiec, M.; Marciniec, B.; Chadyniak, D.; Kasperczyk, J. *J. Mol. Catal. A* **2005**, *225*, 91–101. (d) Balázs, A.; Hetényi, A.; Szakonyi, Z.; Sillanpää, R.; Fülöp, F. *Chem.—Eur. J.* **2009**, *15*, 7376–7381.

(13) Xu, Z.; Chen, Z.; Ye, T. *Tetrahedron: Asymmetry* **2004**, *15*, 355–363.

Scheme 7. Total Synthesis of Palmyrolide A (**3**)



With lactols **17** in hand, the total synthesis of palmyrolide A could now be completed. Following the same synthetic sequence that had proven effective for the synthesis of **1** and *ent*-**2**, lactols **17** were converted to **18** using a similar method to that described previously (Scheme 4). Esterification of alcohol **18** with acid (*R*)-**7** followed by RCM/isomerization gave palmyrolide A (**3**). The spectroscopic data were in full agreement with the data reported in the initial isolation paper[1] and the first total synthesis paper.[3] The optical rotation of (−)-**3** {$[\alpha]_D^{21}$ −27.3 (*c* 0.56, $CHCl_3$)} was in excellent agreement with the isolation report {$[\alpha]_D$−29 (*c* 0.9, $CHCl_3$)}[1] and the first total synthesis {$[\alpha]_D^{21}$ −27 (*c* 0.86, $CHCl_3$)},[3] thereby establishing unequivocally the absolute configuration of the natural product (Scheme 7).

In conclusion, we have completed the total synthesis of two *syn*-configured analogues of palmyrolide A (**1** and *ent*-**2**) that refutes the initially proposed structural assignment of this neuroprotective natural product. Furthermore, we have completed a complementary synthesis of the revised structure **3** that further confirms the reassignment of palmyrolide A by Maio and co-workers.[3] The synthesis of (−)-**3** reported herein proceeds in 10% overall yield (12 steps) which compares favorably with the previous synthesis (7%, 10 steps).[3] This synthetic route will also enable the convergent parallel synthesis of analogues of palmyrolide A and related natural products such as the laingolides,[2a−c] madangolide,[2b] and sanctolide.[2d]

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Supporting Information Available. Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.