First Total Synthesis of Paracaseolide A
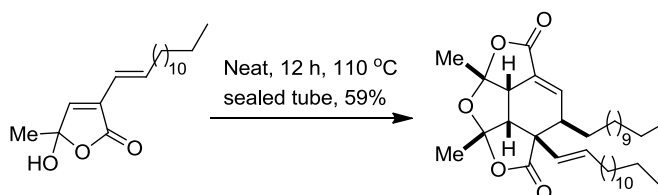
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ABSTRACT

The first total synthesis of the paracaseolide A, a very unusual tetraquinane oxa-cage bislactone recently isolated from the mangrove *Sonneratia paracaseolaris*, has been achieved. The final step and culmination of the eight step synthetic sequence is a [4+2] dimerization of a 4-hydroxybutenolide, generated by singlet oxygen-mediated oxidation of a furan precursor.

An investigation into the stem bark of Chinese mangrove plants, belonging to the genus *Sonneratia*, resulted recently in the isolation by Guo and his coworkers[1] of a very unusual α-alkylbutenolide dimer which was named paracaseolide A (**1**, Scheme 1). Structural elucidation techniques revealed the presence of a rare tetraquinane bislactone skeleton bearing two adjacent linear alkyl chains on the convex face of its oxa-cage-like structure. Natural product **1** showed significant inhibitory activity against dual specificity phosphatase CDC25B, with an IC_{50} value of 6.44 μM.[1] CDC25B is a key enzyme required for cell cycle progression and has been observed in a variety of cancers and is associated with tumor aggressiveness and poor prognosis.[2] Herein, we report the first total synthesis of the highly complex molecular architecture that is paracaseolide A.

The primary goal of our research is to develop methods that provide more efficient and effective responses to synthetic challenges, particularly in the context of traditional intransigent polyoxygenated target structures.[3] Thus, in any given piece of work, we are aiming to achieve as many of the recently delineated[4] and exacting criteria for "ideal synthesis"[5] as possible. Our synthesis of paracaseolide A was developed with these ideas in mind and with the goal of rapidly increasing molecular complexity with minimal use of concessionary steps.[4b] Even the use of the TBS-group is non-traditional as it serves several constructive purposes alongside its more conventional protecting role (*vide infra*).

The isolation team had proposed a very reasonable biosynthetic path for the assembly of paracaseolide A with a [4+2] dimerization of the α-alkenyl-γ-hydroxybutenolide **4** at its heart (Scheme 1). We would like to add to the proposal that a concerted Diels–Alder[6] cycloaddition of the

[1] Chen, X.-L.; Liu, H.-L.; Li, J.; Xin, G.-R.; Guo, Y.-W. *Org. Lett.* **2011**, *13*, 5032.

[2] Lammer, C.; Wagerer, S.; Saffrich, R.; Mertens, D.; Ansorge, W.; Hoffmann, I. *J. Cell Sci.* **1998**, *111*, 2445.

[3] (a) Montagnon, T.; Tofi, M.; Vassilikogiannakis, G. *Acc. Chem. Res.* **2008**, *41*, 1001. (b) Noutsias, D.; Alexopoulou, I.; Montagnon, T.; Vassilikogiannakis, G. *Green Chem.* **2012**, *14*, 601.

[4] (a) Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193. (b) Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657. (c) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010.
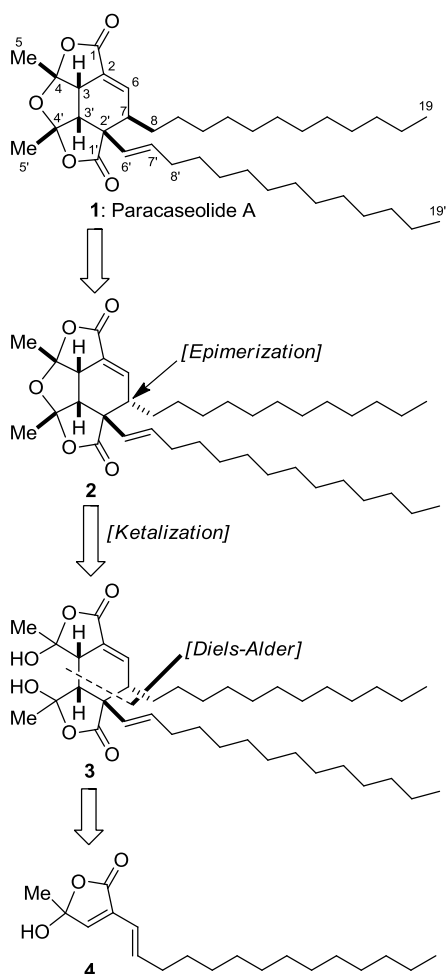
[5] For the first introduction to the "ideal synthesis" concept, see: Hendrickson, J. B. *J. Am. Chem. Soc.* **1975**, *97*, 5784.

[6] For a review of the use of the Diels–Alder reaction in synthesis, see: (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. E. *Angew. Chem. Int. Ed.* **2002**, *41*, 1668. For review & discussion of

Scheme 1. Retrosynthetic Analysis

1: Paracaseolide A

[Epimerization]

2

[Ketalization]

[Diels-Alder]

3

4

Scheme 2. Synthesis of the Dimerization Precursor α-Alkenyl-γ-hydroxybutenolide **4**

I$_2$, PPh$_3$, imid., CH$_2$Cl$_2$
0.5 h, rt, 98%

5 → **6**

t-BuLi
Et$_2$O, 2.5 h
-78 ^{0}C to rt, 96%

7 → **8**

TBSCl, imid., 4-DMAP
DMF, 12 h, rt, 84%

HMPA, n-BuLi, THF
0.5 h, 0 ^{0}C to rt, 96%

9 → **10**

p-TsOH, toluene
12 h, 110 ^{0}C, 78%

n-BuLi, MeI, THF
2.5 h, 0 ^{0}C to rt, 84%

11 → **4**

O$_2$, MB, hv, CH$_2$Cl$_2$
5 min, 0 ^{0}C, 52%

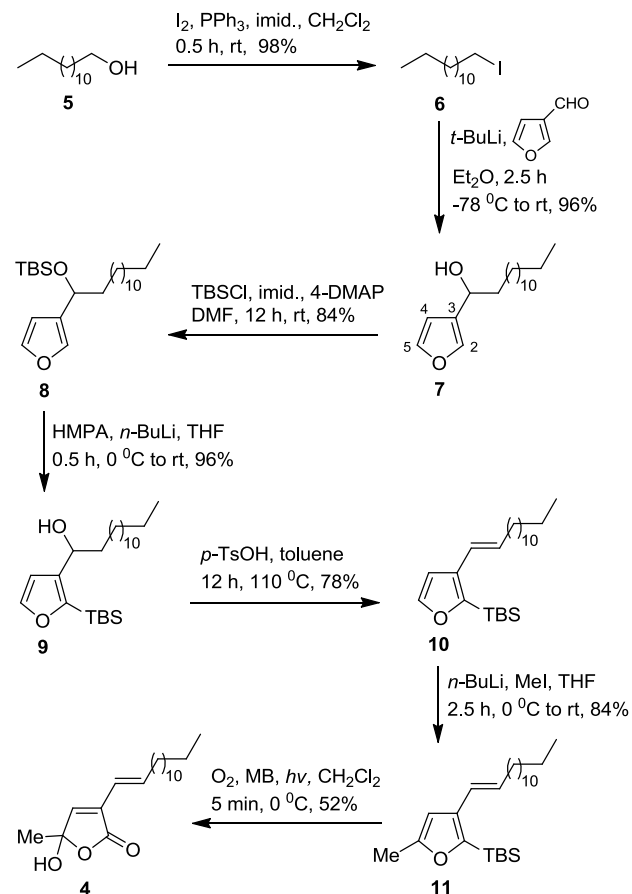
starting E,E-diene **4** would be expected to afford the C7 diastereoisomer of the natural product, compound **2** (Scheme 1). Although a stepwise Diels–Alder reaction cannot be excluded, we believe that a concerted Diels–Alder reaction might be occurring followed by a fast epimerization of the readily epimerizable C7-centre of the initially formed diastereoisomer **2**, leading to the formation of the natural compound **1** (Scheme 1). This type of epimerization should be thermodynamically favored since it repositions the long linear alkyl chain (appended at C7), from the concave, to the convex face of the cage-like structure. Following these considerations, our synthetic design (Scheme 1) hinged upon the use of this bioinspired [4+2]-Diels–Alder dimerization of α-alkenyl-γ-hydroxybutenolide **4**, and, as such, it followed in the footsteps of other successful and elegant syntheses

that have utilized Diels–Alder-dimerizations to access complicated architectures.[7] It was anticipated that the α-

biomimetic Diels–Alder strategies, see: (b) de la Torre, M. C.; Sierra, M. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 160. (c) Stocking, E. M.; Williams, R. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 3078. For a review of Diels–Alder-type natural products, see: (d) Ichihara, A.; Oikawa, H *Curr. Org. Chem.* **1998**, *2*, 365.

[7] For representative examples since 1999, see: (a) Simon, O.; Reux, B.; La Clair, J. J.; Lear, M. J. *Chem. Asian J.* **2010**, *5*, 342. (b) Dong, S.; Zhu, J.; Proco, J. A. Jr. *J. Am. Chem. Soc.* **2008**, *130*, 2738. (c) Pouységu, L.; Chassaing, S.; Dejugnac, D.; Lamidey, A.-M.; Miqueu, K.; Sotiropoulos, J.-M.; Quideau, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 3552. (d) Nicolaou, K. C.; Lim, Y. H.; Piper, J. L.; Papageorgiou, C. D. *J. Am. Chem. Soc.* **2007**, *129*, 4001. (e) Shiina, J.; Oikawa, M.; Nakamura, K.; Obata, R.; Nishiyama, S. *Eur. J. Org. Chem.* **2007**, 5190. (f) Lebrasseur, N.; Gagnepain, J.; Ozanne-Beaudenon, A.; Léger, J. M.; Quideau, S. *J. Org. Chem.* **2007**, *72*, 6280. (g) Gagnepain, J.; Méreau, R.; Dejugnac, D.; Léger, J.-M.; Castet, F.; Deffieux, D.; Pouységu, L.; Quideau, S. *Tetrahedron* **2007**, *63*, 6493. (h) Gagnepain, J.; Castet, F.; Quideau, S. *Angew. Chem. Int. Ed.* **2007**, *46*, 1533. (i) Porco, J. A. Jr.; Su, S.; Lei, X.; Bardhan, S.; Rychnovsky. S. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 5790. (j) Mehta, G.; Chandra Pan, S. *Org. Lett* **2004**, *6*, 3985. (k) Lei, X.; Johnson, R. P.; Proco, J. A. Jr. *Angew. Chem. Int. Ed.* **2003**, *42*, 3913. (l) Li, C.; Johnson, R. P.; Porco, J. A. Jr. *J. Am. Chem. Soc.* **2003**, *125*, 5095. (m) Shoji, M.; Yamaguchi, J.; Kakeya, H.; Osada, H.; Hayashi, Y. *Angew. Chem. Int. Ed.* **2002**, *41*, 3192. (n) Li, C.; Bardhan, S.; Pace, E. A.; Liang, M.-C.; Gilmore, T. D. Porco, J. A. Jr. *Org. Lett.* **2002**, *4*, 3267. (o) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773. (p) Li, C.; Lobkovsky, E.; Porco, J. A. Jr. *J. Am. Chem. Soc.* **2000**, *122*, 10484. (q) Nicolaou, K. C.; Vassilikogiannakis, G.; Simonsen, K. B.; Baran, P. S.; Zhong, Y.-L., Vidali, V. P.; Pitsinos, E. N.; Couladouros, E. A. *J. Am. Chem. Soc.* **2000**, *122*, 3071. (r) Nicolaou, K. C.; Simonsen, K. B.; Vassilikogiannakis, G.; Baran, P. S.; Vidali, V. P.; Pitsinos, E. N.; Couladouros, E. A. *Angew. Chem. Int. Ed.* **1999**, *38*, 3555.

alkenyl-γ-hydroxybutenolide **4** could be accessed through the singlet oxygen photooxygenation of an appropriately substituted furan precursor.

With this in our minds our investigation began with synthesis of the requisite furan photooxygenation precursor **11** which was accomplished as shown in Scheme 2. Lithium-halogen exchange of 1-iodotridecane (**6**) followed by addition to 3-furaldehyde resulted in the formation of furanol **7**. The resultant hydroxyl functionality then served another useful purpose when it was utilized to effect a regioselective silylation of the furan (at the 2-position as opposed to the less hindered 5-position, **7** → **9**) Specifically, 3-(α-trialkylsilyloxy)alkyl-furan **8** underwent a [1,4] O→C silyl migration[8] to furnish 2-trialkylsilyl-3-(α-hydroxy)alkyl-furan **9** (Scheme 2). After acidic dehydration using *p*-TsOH, the remaining unsubstituted *ortho*-position of the furan was methylated using standard conditions to afford the photooxygenation precursor furan **11**. The presence of the TBS group at the 2-position of the furan not only guaranteed the regioselective methylation of position-5, it also directed the regioselectivity of the singlet oxygen ($^1O_2$) oxidation[9] such that it yielded exclusively the requisite α-substituted γ-hydroxybutenolide **4**. In contrast to this clear and desired regioselective outcome, it is well known that γ-hydroxybutenolides prepared by photooxygenation of 3-alkyl furans are mixtures of α- and β-alkyl γ-hydroxybutenolides,[10a-c] or solely the β-regioisomers when Hunig' s base is included.[10c-j] Thus, through a short and high yielding synthetic sequence, α-alkenyl-γ-hydroxybutenolide **4** was synthesized.

With the monomer **4** in-hand, the stage was now set to explore the ambitious bioinspired [4+2] dimerization/ketalization/epimerization sequence to reach our target, paracaseolide A. Unfortunately, heating of a toluene solution of **4** at 110 ºC in a sealed tube for 12 h, resulted in formation of the α,γ-disubstituted butenolide **13** in 42% isolated yield (Scheme 3). A mechanistic explanation for the formation of compound **13** invokes an intramolecular *oxa*-Michael type addition of the

Scheme 3. Bioinspired [4+2] Dimerization of 4-Hydroxybutenolide **4** to Paracaseolide A
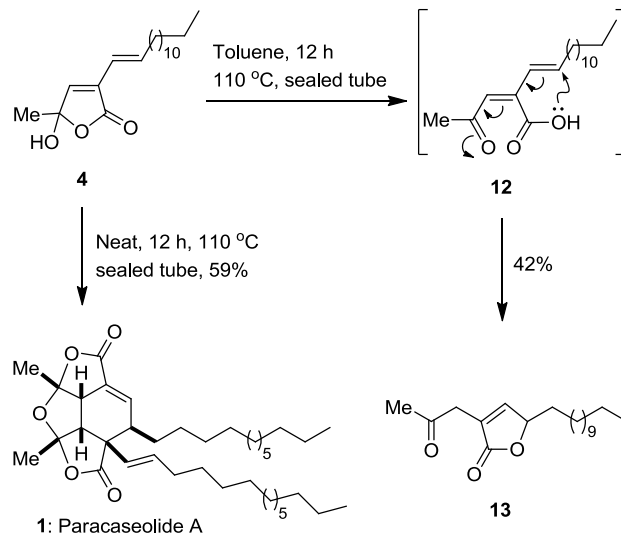
open keto-acid form **12** is shown in Scheme 3. In order to avoid this unwanted reaction (**4** → **13**) and favor the desired bimolecular [4+2] dimerization, we opted to investigate increasing the concentration. To our satisfaction when the reaction was performed neat in a sealed tube at 110 ºC for 12 h, formation of 3:1 mixture of the natural product paracaseolide A (**1**) *vs* the α,γ-disubstituted butenolide **13** was observed by ^{1}H NMR analysis of the crude reaction mixture. Chromatographic separation of the two products afforded the clean natural product **1** in 59% isolated yield.

In summary, an extremely short (8 steps in total, starting from commercially available compounds), fast (executed easily in 4-5 days) and efficient protocol (15% overall yield) has been developed for the first total synthesis of paracaseolide A (**1**). The synthetic sequence involves transformation of a simple and readily accessible furan substrate into the desired 4-hydroxybutenolide **4** using a singlet oxygen-mediated oxidation.[3,11] This 4-hydroxybutenolide is the precursor for the final bioinspired [4+2]-dimerization/ketalization/epimerization that gives rise to the natural product paracaseolide A. This atom-[12] and step-economic[13] protocol, which utilizes

[8] Bures, E. J.; Keay, B. A. *Tetrahedron Lett.* **1987**, *28*, 5965.

[9] For the silyl stabilization concept, see: (a) Adam, W.; Rodriguez, A. *Tetrahedron Lett.* **1981**, *22*, 3505. For use in synthesis of 4-hydroxybutenolides see: (b) Katsumura, S.; Hori, K.; Fujiwara, S.; Isoe, S. *Tetrahedron Lett.* **1985**, *26*, 4625. (c) Sofikiti, N.; Tofi, M.; Montagnon, T.; Vassilikogiannakis G.; Stratakis, M. *Org. Lett.* **2005**, *7*, 2357. For direct comparisons between the photoxygenations of silyl- and unsubstituted furans, see: (d) Kernan, M. R.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 2773. (e) Bury, P.; Hareau, G.; Kocieński, P.; Dhanak, D. *Tetrahedron* **1994**, *50*, 8793. (f) Shiraki, R.; Sumino, A.; Tadano, K.; Ogawa, S. *J. Org. Chem.* **1996**, *61*, 2845.

[10] For representative examples see: (a) Held, C.; Fröhlich, R.; Metz, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 1058. (b) de la Torre, M. C.; García, I.; Sierra, M. A. *J. Nat. Prod.* **2002**, *65*, 661. (c) Held, C.; Fröhlich, R.; Metz, P. *Adv. Synth. Catal.* **2002**, *344*, 720. (d) Demeke, D; Forsyth, C. J. *Tetrahedron* **2002**, *58*, 6531. (e) Brohm, D.; Philippe, N.; Metzger, S.; Bhargava, A; Müller, O.; Lieb, F.; Waldmann, H. *J. Am. Chem. Soc.* **2002**, *124*, 13171. (f) Demeke, D.; Forsyth, C. J. *Org. Lett.* **2003**, *5*, 991. (g) Miyaoka, H.; Yamanishi, M.; Kajiwara, Y.; Yamada, Y. *J. Org. Chem.* **2003**, *68*, 3476. (h) Cheung, A. K.; Murelli, R.; Snapper, M. L. *J. Org. Chem.* **2004**, *69*, 5712. (i) Izzo, I.; Avallone, E.; Della Monica, C.; Casapullo, A.; Amigo, M.; De Riccardis, F. *Tetrahedron* **2004**, *60*, 5587. (j) Basabe, P.; Delgado, S.; Marcos, I. S.; Diez, D.; Diego, A.; De Román, M.; Urones, J. G. *J. Org. Chem.* **2005**, *70*, 9480.

[11] For furan photooxidations see: (a) Foote, C. S.; Wuesthoff, M. T.; Wexler, S.; Burstain, I. G.;. Denny, R.; Schenck, G. O.; Schulte-Elte, K. H. *Tetrahedron* **1967**, *23*, 2583. (b) Gollnick, K.; Griesbeck, A. *Tetrahedron* **1985**, *41*, 2057. (c) Feringa, B. L. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 469. (d) Vassilikogiannakis, G.; Stratakis, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 5465. (e) Georgiou, T.; Tofi, M.; Montagnon, T.; Vassilikogiannakis, G, *Org. Lett.* **2006**, *8*, 1945. (f) Montagnon, T.; Noutsias, D.; Alexopoulou, I.; Tofi, M.; Vassilikogiannakis, G. *Org. Biomol. Chem.* **2011**, *9*, 2031. (g) Vassilikogiannakis, G.; Alexopoulou, I.; Tofi, M.; Montagnon, T. *Chem. Commun.* **2011**, *47*, 259. (h) Kouridaki, M.; Montagnon, T.; Tofi, M; Vassilikogiannakis, G. *Org. Lett.* **2012**, *14*, 2374.

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[13] Wender, P. A.; Miller, B. L. *Nature* **2009**, *460*, 197.

environmentally-benign oxygen from the air as the oxidant, and, which uses a bioinspired [4+2]-cycloaddition to accomplish rapid increase of molecular complexity in one synthetic operation, represents an achievement that takes us a step, albeit a small one, towards achieving the prized goal of an ideal synthesis.[4]

Supporting Information Available: Experimental procedures, full spectroscopic data and copies of ^{1}H and ^{13}C-NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.