ORGANIC LETTERS

2011
Vol. 13, No. 15
3980–3983

Synthesis of the Tricyclic Core of Labiatin A and Australin A

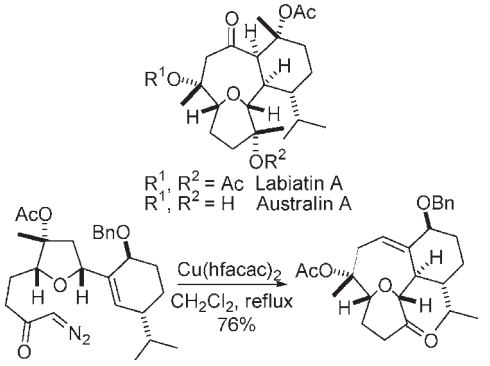
J. Stephen Clark,* David Vignard, and Andrew Parkin

WestCHEM, School of Chemistry, University of Glasgow, Joseph Black Building, University Avenue, Glasgow G12 8QQ, United Kingdom

stephen.clark@glasgow.ac.uk

Received June 3, 2011

ABSTRACT



A concise synthesis of the tricyclic core of the marine diterpene natural products labiatin A and australin A has been accomplished. The key ring-forming transformation is a cascade reaction comprising generation of a copper carbenoid from a diazo ketone, intramolecular reaction of the carbenoid with a cyclic ether, and rearrangement of the resulting free oxonium ylide or its metal-bound equivalent with ring expansion of the original cyclic ether.

Labiatin A and australin A are members of the cladiellin (eunicillin) family of marine diterpene natural products. These compounds differ structurally from the other cladiellins in that they possess an ether bridge between C-2 and C-6 (cladiellin numbering) rather than the usual C-2−C-9 ether linkage (Figure 1).[1] Neither of these natural products has been the subject of published synthetic endeavors by other research groups, and so they present new challenges to those working in the area of marine diterpene synthesis.

Labiatin A was first isolated from extracts of the gorgonian *Eunicella Labiata* collected by Fenical and co-workers in the Atlantic Ocean off the coast of Senegal.[2] Fenical and co-workers determined the structure of labiatin A, apart from its absolute configuration, along with those of four other cladiellins—labiatins B and C and labiatamides A and B—isolated from the same source. Labiatin A was found to be structurally anomalous because it possesses a C-2−C-6 ether bridge instead of the C-2−C-9 ether linkage found in the other diterpenes isolated from the same sample of *Eunicella Labiata*. Although bioactivity data for labiatin A were not disclosed by Fenical and co-workers, labiatin B was reported to exhibit significant cytotoxicity against human colon cancer cells (HCT-116; $ED_{50} = 0.85\ \mu g\ mL^{-1}$).[2]

In 2005, Sheu and co-workers reported the structural characterization (absolute stereochemistry excepted) of a group of new cladiellin natural products isolated from extracts of the soft coral *Cladiella australis* collected off the south coast of Taiwan and named them australins A−D.[3] Interestingly, australins A and D possess the same unusual C-2−C-6 ether bridged core structure as labiatin A. In fact, australin A is simply the doubly deacetylated analogue of labiatin A, possessing free hydroxyl groups at C-3 and C-7. Biological evaluation of australins B and D revealed that australin B has modest cytotoxic activity and that australin D has weak activity against MDA-MB-231 cells ($ED_{50} = 24.4\ \mu g\ mL^{-1}$).[3] Very recently, four additional members of the australin family (E−H) possessing the unusual C-2−C-6

(1) (a) Bernardelli, P.; Paquette, L. A. *Heterocycles* **1998**, *49*, 531–556. (b) Sung, P.-J.; Chen, M.-C. *Heterocycles* **2002**, *57*, 1705–1715.

(2) Roussis, V.; Fenical, W.; Vagias, C.; Kornprobst, J.-M.; Miralles, J. *Tetrahedron* **1996**, *52*, 2735–2742.

(3) Ahmed, A. F.; Wu, M.-H.; Wang, G.-H.; Wu, Y.-C.; Sheu, J.-H. *J. Nat. Prod.* **2005**, *68*, 1051–1055.

10.1021/ol201498g
Published on Web 07/06/2011

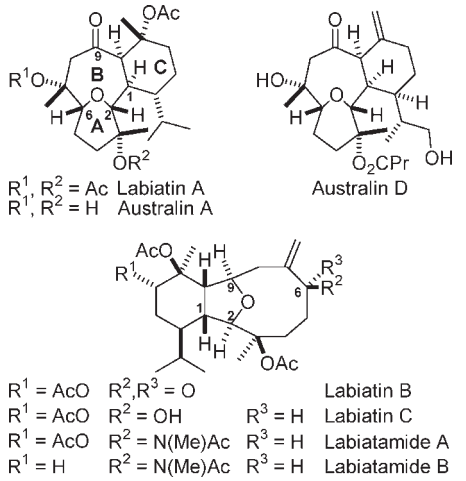


Figure 1. A selection of labiatins, labiatamides, and australins.

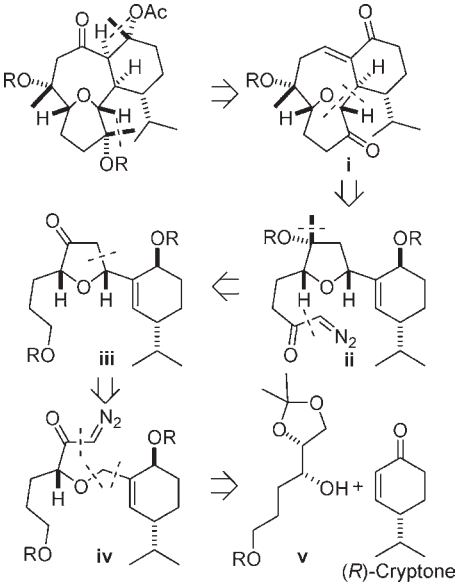
ether bridged core have been isolated from a *Cladiella* species and one of them (australin E) has been shown to activate the inositol 5-phosphate SHIP1 *in vitro*.[4]

We became interested in the synthesis of labiatin A and australin A as part of our wider research program concerning the development of a completely general and flexible approach to the synthesis of the entire cladiellin family of natural products.[5,6] In particular, we wanted to discover whether our recently developed synthetic strategy could be applied to the synthesis of labiatin A and australin A and our key ring-forming reaction could be used to construct the AB ring system while simultaneously grafting this onto the preformed C ring.

Our retrosynthetic analysis was guided by previous model studies (Scheme 1).[7] It commences with removal of the acetate groups, disconnection of two of the methyl groups, and replacement of the ring B carbonyl group with a C-9−C-10 alkene to give the diketone **i**. Disconnection of the A and B rings by recognition of the key rearrangement of an oxonium ylide or a metal-bound equivalent in the forward direction leads to the diazo ketone **ii**. Removal of the methyl (C-16) and diazo groups gives the simple dihydrofuranone **iii**, and disconnection of the ring by identification of a carbenoid C−H insertion reaction in the forward direction leads to the diazo ketone **iv**. Removal of the diazo group and disconnection of the ether linkage reveals the alcohol **v** and (*R*)-cryptone as starting materials.

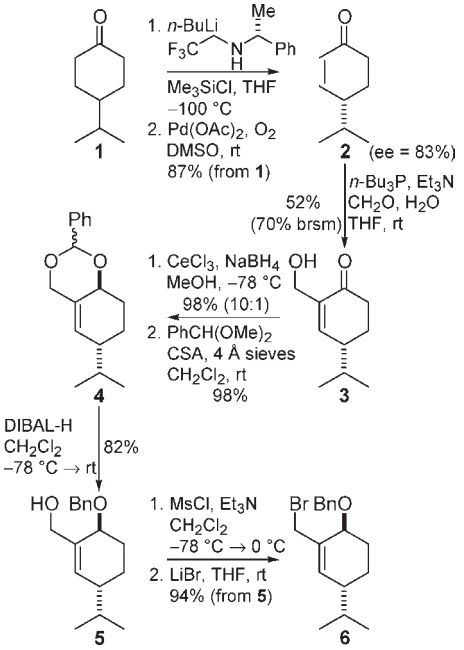
Synthesis of the tricyclic core commenced with construction of ring C (Scheme 2). The commercially available enone **1** was converted into (*R*)-cryptone (**2**) in high ee by

Scheme 1. Retrosynthetic Analysis of Labiatin A



enantioselective deprotonation with Koga's base[8] and *in situ* enolate quench with trimethylsilyl chloride and then Saegusa oxidation of the resulting silyl enol ether using a substoichiometric amount of palladium(II) acetate.[9] (*R*)-Cryptone (**2**) was then subjected to a Morita−Baylis−Hillman reaction with formaldehyde to give the hydroxyenone **3**.[10] The reaction failed to reach completion, but (*R*)-cryptone was recovered and resubmitted to the reaction. Luche reduction converted the hydroxyenone **3** into the corresponding diol (10:1 dr), and the major diastereomer was then transformed into the benzylidene acetal **4**. Regioselective acetal reduction

Scheme 2. Enantioselective Synthesis of Ring C



(4) Williams, D. E.; Amlani, A.; Dewi, A. S.; Patrick, B. O.; van Ofwegen, L.; Mui, A. L.-F.; Andersen, R. J. *Aust. J. Chem.* **2010**, *63*, 895–900.

(5) Clark, J. S.; Hayes, S. T.; Wilson, C.; Gobbi, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 437–440.

(6) Clark, J. S.; Berger, R.; Hayes, S. T.; Thomas, L. H.; Morrison, A. J.; Gobbi, L. *Angew. Chem., Int. Ed.* **2010**, *49*, 9867–9870.

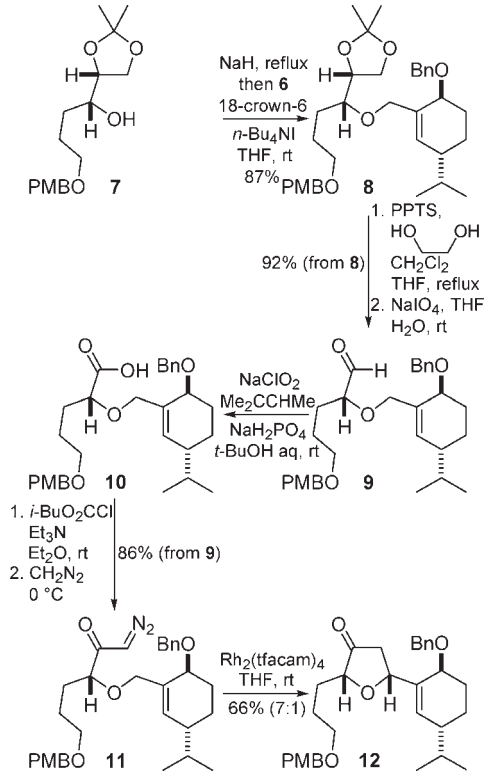
(7) Clark, J. S.; Baxter, C. A.; Castro, J. L. *Synthesis* **2005**, 3398–3404.

(8) Aoki, K.; Koga, K. *Tetrahedron Lett.* **1997**, *38*, 2505–2506.

using DIBAL-H[11] gave the alcohol **5**, and this was converted into the bromide **6** via the corresponding mesylate.

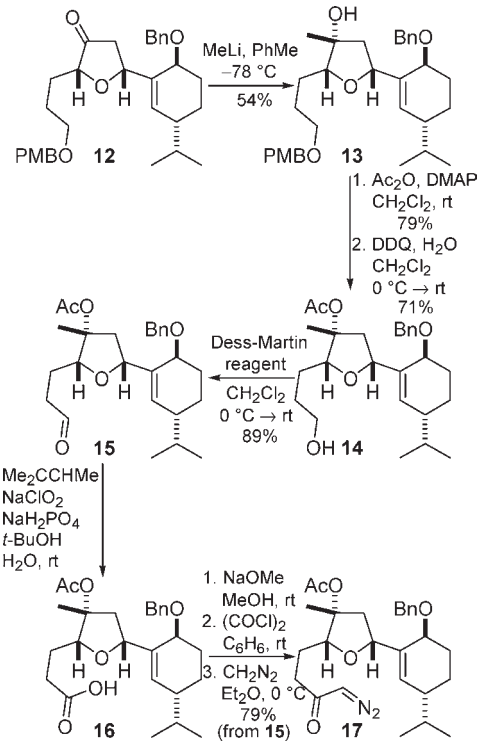
The alcohol **7**, prepared from D-mannitol using a procedure described by us previously,[12] was coupled to the bromide **6** using standard etherification conditions (Scheme 3). The resulting ether (**8**) was then treated with pyridinium *p*-toluenesulfonate (PPTS) in ethylene glycol to cleave the acetonide, and the resulting 1,2-diol was subjected to periodate cleavage to furnish the aldehyde **9**. Oxidation[13] gave the carboxylic acid **10**, and this was converted into the diazo ketone **11** by formation of a mixed anhydride and subsequent treatment with diazomethane. The carbenoid C−H insertion reaction was performed using rhodium(II) trifluoroacetamide in THF at room temperature.[7] The reaction delivered a diastereomeric mixture of dihydrofuranones (66% yield; 7:1 favoring **12**) resulting from insertion at the allylic site adjacent to the ether. Diastereomers were not separated, and the mixture was used directly in the next reaction.

Scheme 3. Fragment Coupling and Dihydrofuranone Formation



The dihydrofuranone **12** was treated with methyl lithium at low temperature to deliver a mixture (8:1) of alcohols from which the alcohol **13** was isolated in 54% yield (Scheme 4). Acetylation of the alcohol **13** followed by removal of the PMB group using DDQ afforded the alcohol **14**. Dess−Martin oxidation of this alcohol to give the aldehyde **15** followed by Pinnick-type oxidation delivered the carboxylic acid **16**.[13] Deprotonation of the carboxylic acid and reaction with oxalyl chloride afforded the acid chloride which was immediately treated with diazomethane to deliver the diazo ketone **17**.

Scheme 4. Construction of the Key Cyclization Precursor



The construction of the diazo ketone **17** allowed the pivotal carbenoid cyclization reaction to be investigated (Scheme 5). Treatment of the substrate **17** with copper(II) hexafluoroacetylacetonate in dichloromethane at reflux resulted in formation of the required tricyclic ketone **18** in 76% yield as a single stereoisomer, in contrast to the outcome of related reactions and that of the model substrate.[7] The reaction is believed to proceed by generation of a copper carbenoid followed by reaction of this highly reactive electrophilic species with the ether-oxygen and subsequent ring-expanding [2,3] rearrangement of a free oxonium ylide or reorganization of its metal-bound equivalent to give the ketone **18**.[12,14−16] The methyl group at C-3 (C-15) was then installed in a highly stereoselective manner by treatment of the ketone **18** with MeLi at −78 °C to give the tertiary alcohol **19** as a single isomer, the

(9) (a) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011–1013. (b) Larock, R. C.; Hightower, T. R.; Kraus, G. A.; Hahn, P.; Zheng, D. *Tetrahedron Lett.* **1995**, *36*, 2423–2426.

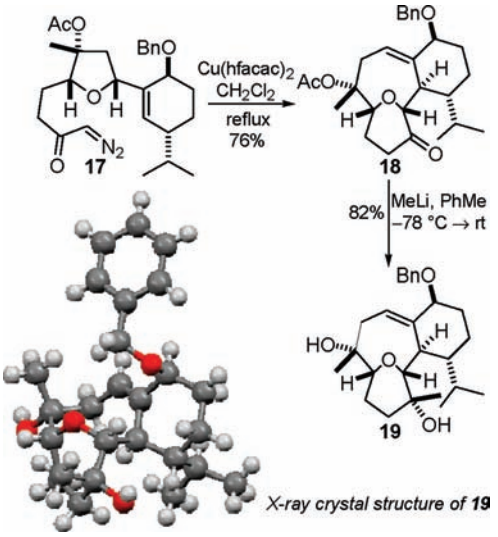
(10) Kabat, M. M.; Kiegel, J.; Cohen, N.; Toth, K.; Wovkulich, P. M.; Uskoković, M. R. *J. Org. Chem.* **1996**, *61*, 118–124.

(11) Schreiber, S. L.; Wang, Z.; Schulte, G. *Tetrahedron Lett.* **1988**, *29*, 4085–4088.

(12) Clark, J. S.; Baxter, C. A.; Dossetter, A. G.; Poigny, S.; Castro, J. L.; Whittingham, W. G. *J. Org. Chem.* **2008**, *73*, 1040–1055.

(13) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096.

Scheme 5. Formation of the Complete Tricyclic Core **19** of Labiatin A and Australin A



structure of which was confirmed by X-ray crystallography (Scheme 5).

In summary, an advanced intermediate for the synthesis of the marine natural products labiatin A and australin A has been constructed in 21 steps. Rearrangement of a catalytically generated oxonium ylide or its metal-bound equivalent has been used to construct the tricyclic core possessing a C-2–C-6 ether bridge instead of the C-2–C-9 ether linkage found in most other cladiellin natural products. Further studies concerning the total synthesis of the labiatins and australins will be reported in due course.

Acknowledgment. WestCHEM and the University of Glasgow for funding (D.V.). We thank Dr. Louis Farrugia (University of Glasgow) for assistance with X-ray crystallography data.

Supporting Information Available. Spectroscopic and other data for compounds **2**–**6**, **8**, **9**, **11**–**15**, **17**–**19** plus X-ray data (CIF files) for compound **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

(14) (a) Clark, J. S.; Krowiak, S. A.; Street, L. J. *Tetrahedron Lett.* **1993**, *34*, 4385–4388. (b) Clark, J. S.; Whitlock, G.; Jiang, S.; Onyia, N. *Chem. Commun.* **2003**, 2578–2579.

(15) West, F. G.; Naidu, B. N.; Tester, R. W. *J. Org. Chem.* **1994**, *59*, 6892–6894.

(16) Karche, N. P.; Jachak, S. M.; Dhavale, D. D. *J. Org. Chem.* **2001**, *66*, 6323–6332.