Natural Products

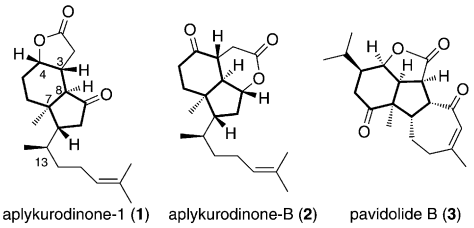
DOI: 10.1002/ange.201301465

Formal Enantioselective Synthesis of Aplykurodinone-1**

*Philippe A. Peixoto, Alexandre Jean, Jacques Maddaluno, and Michaël De Paolis**

Dedicated to Professor Kozo Shishido

Aplykurodinone-1 (**1**) is a degraded sterol that can be isolated from the skin of *Syphonota geographica*, a mollusc that belongs to the Aplysiidae family (Scheme 1).[1] While the



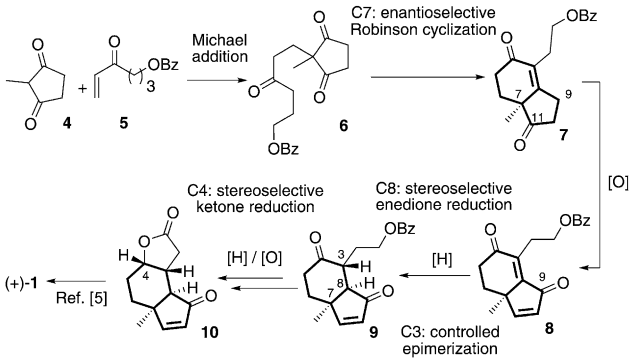
Scheme 1. Molecules containing a hydrindane framework.

biological profile of this molecule remains unknown to date, the closely related aplykurodinone-B (**2**) exhibits mild cytotoxic activities.[2] Noteworthy, the structure of **1** features six contiguous stereocenters, including a stereogenic quaternary center, embedded in an intriguing hydroindenone system. As a typical feature of steroids, aplykurodinones contain a lipophilic side chain with the stereocenter at C13 connected to the core. On the other hand, this class of molecules features a *cis* hydrindane moiety (C7–C8 configuration), a structural framework that is also found in pavidolide B (**3**).[3]

The continued interest in steroids[4] is highlighted by a recent total synthesis of *rac*-**1** by Danishefsky and coworkers, who employed an elegant strategy featuring an ionic Diels–Alder reaction to form the racemic hyndrindane core.[5]

"Hajos–Parrish-type" ketones[6] are versatile scaffolds for the formation of complex target molecules, as they are often available in enantioenriched form.[7] As part of our current program of natural product synthesis, we were interested in the development of an oxidative process to expand the potential of the Hajos–Parrish methodology to the synthesis of chiral hydrindenediones with quaternary carbon stereocenters.[8] Herein, we report the successful implementation of this strategy, resulting in the concise formal enantioselective synthesis of **1**.

The structure of **1** inspired a synthetic approach in which the formation of the quaternary carbon center C7 is pivotal to the stereoselective assembly of the complete skeleton (Scheme 2). In accordance with this plan, we envisaged the



Scheme 2. Synthetic plan toward (+)-**1**. Bz = Benzoyl.

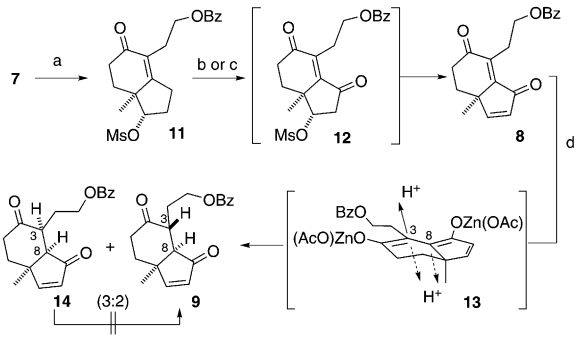
preparation of **7** by Michael coupling of **4** and **5**, followed by the enantioselective Robinson annulation of adduct **6**. Next, oxidation of **7** at C9 followed by the formal deoxygenation at C11 was planned in order to access **8**. A chemoselective reduction of the olefin would lead to the stereocenters at C8 and C3 in **9**. Our assumptions were that the *cis* relationship at C8–C7 could be thermodynamically favored, while the *trans* relationship at C8–C3 could be changed by epimerization. Then, chemo- and diastereoselective reduction of **9** followed by oxidative lactonization would lead to the known tricyclic system **10**. Overall, the stereocenter at C7 of **7** would control the formation of the three other stereogenic centers.

To evaluate this strategy, *rac*-**7** was produced on a multigram scale from readily available **4** and **5**.[9] In order to perform the formal deoxygenation of **7**, the reduction of the ketone moiety at C11 was followed by the mesylation of the resulting hydroxy group to facilitate the elimination step (Scheme 3). Regarding the oxidation of C9, we anticipated that a dienolate formed in the presence of bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) would steer the regioselectivity of the process. As it is compatible with this base, molecular oxygen was the best oxidant for trapping the dienolate, both in terms of practicability and regioselectivity. Pleasingly, a screening of different conditions revealed that exposure of **11** to DBU (1 equiv) in refluxing toluene under an oxygen atmosphere allowed the isolation of **8** in 40% yield.[9] In the absence of oxygen, the starting material was

[*] Dr. P. A. Peixoto, A. Jean, Dr. J. Maddaluno, Dr. M. De Paolis
CNRS, Laboratoire COBRA, UMR 6014 and FR 3038
Université et INSA de Rouen
76821 Mont Saint Aignan (France)
E-mail: michael.depaolis@univ-rouen.fr
Homepage: http://ircof.crihan.fr/

[**] We are grateful to the Région Haute-Normandie for generous support and to Morgan Cormier for valuable technical assistance. Helpful discussions with Prof. H. Kotsuki (Kochi University, Japan) are acknowledged. Dedicated to Prof. K. Shishido on the occasion of the 2013 Award of the Pharmaceutical Society of Japan.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201301465.



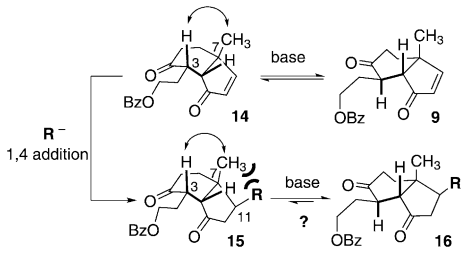
Scheme 3. Reagents and conditions: a) $NaBH_4$, MeOH, −40 °C; MsCl, CH_2Cl_2, RT, 80% over steps; b) DBU (1 equiv), PhMe, 120 °C, O_2, 120 h, [**11**] = 0.3 M, 40%; c) DBU (2 equiv), $Cu(OAc)_2$ (10 mol%), CH_2Cl_2, RT, O_2, 3 h 30, [**11**] = 0.025 M, 52%; d) Zn (2.5 equiv), AcOH, RT, 79% of **14**:**9** (3:2). MsCl = methanesulfonyl chloride.

recovered, implying that ketone **12** was formed first, and the oxidation of C9 was followed by the elimination of the mesylate.[10] Although the efficiency of the process remained low, the unprecedented directed and metal-free aerobic oxidation/deoxygenation was demonstrated.[11]

To improve the efficiency of the process, different catalysts were screened. Pleasingly, the combination of $Cu(OAc)_2$ (0.1 equiv) and DBU (2 equiv) under an atmosphere of oxygen afforded **8** (52%) after reaction for only a few hours at room temperature.[12] Again, when the reaction was performed without oxygen, the starting material was recovered, thus indicating that the formation of ketone **12** is the first step of this process.[10] While the γ-oxidation of γ,δ-unsaturated ketones by copper(II)–amine complexes is known,[13] there is no precedent for similar oxidations with less acidic α,β-unsaturated ketones. To our knowledge, the disclosed methodology is therefore the first example of a directed and aerobic oxidation of hydroindenone in one pot without preformation of a dienolate using an inexpensive and ecologically benign catalyst.

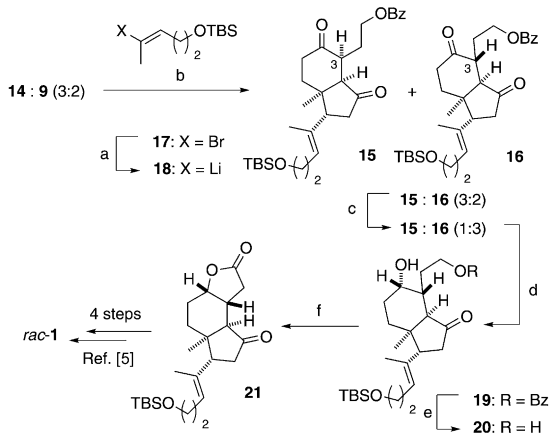
With large quantities of **8** at our disposal, we turned our attention to the chemo- and stereoselective reduction of the enedione moiety, for which a smooth reductant was needed. Upon treatment of **8** with zinc dust in acetic acid, the chemoselective reduction proceeded in 79% yield via enolate **13**. Out of four possible isomers, only **14** and **9** were produced in a 3:2 ratio.[14] Importantly, both products were the result of a stereoselective protonation of C8 from the convex side of the bicyclic motif, thus enabling access to functionalized *cis*-hydrindane structures directly from Hajos–Parrish-type ketones in two steps. Unfortunately, numerous attempts to convert **14** to **9** through epimerization met with failure. Indeed, **14** remained the major isomer after the treatment of a mixture of **14** and **9** under various basic or acidic conditions, while the decomposition of the materials was observed upon heating.[9]

Prompted to revise our initial strategy, we hypothesized that a structural modification of **14**/**9** could steer the epimerization toward the formation of the *trans* isomer. We initially assumed that 1,3-diaxial interactions would destabilize **14** (Scheme 4). However, this destabilization proved



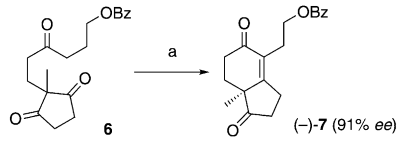
Scheme 4. Comparison of epimerization of **14** and **15**.

insufficient to shift the base-triggered equilibrium toward **9**. Methods to enhance these interactions could involve the introduction of a substituent at C11 to exert vicinal repulsion, as in **15**. Provided the two substituents (R and CH_3) are in a *cis* configuration, the resulting repulsion could enhance the 1,3-diaxial interactions (C7/C3) and efficiently drive the base-promoted epimerization toward **16**. Incidentally, the implementation of this strategy was an opportunity to graft the side chain of **1**. Hence, the 1,4 addition of the pendant vinyl moiety **18** to **14**/**9** (3:2) furnished **15**/**16** (3:2) in 58% yield with facial selectivity (Scheme 5).[15]



Scheme 5. Reagents and conditions: a) **17**, *t*BuLi, Et_2O, −78 °C; b) CuCN, Et_2O/THF, −78 °C, 58%; c) DBU (5 equiv), THF, RT, 94% of **15**:**16** (1:3); d) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −78 °C; e) $LiOH \cdot H_2O$, THF/H_2O/MeOH, RT; f) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, RT, 36% over three steps. TBS = *tert*-butyldimethylsilyl, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy.

Gratifyingly, treatment of the mixture **15**/**16** (3:2) with DBU shifted the equilibrium significantly toward **16** (**15**/**16**, 1:3, 94% yield). Once our epimerization strategy was validated, we turned our attention to the reduction of the ketone moiety at C4. Pleasingly, the combination of $CeCl_3 \cdot H_2O$ and $NaBH_4$ was found to reduce **16** in a chemo- and stereoselective manner. After removal of the benzoate group of **19**, the stage was set for the oxidative lactonization of diol **20**. Oxidation of the primary hydroxy group and the lactol moiety by applying the conditions described by Forsyth and co-workers[16] provided lactone **21**. Importantly, **21** was isolated as a single isomer in 36% overall yield (three steps from **15**/**16**) with spectroscopic data in agreement with those reported.[9] From **21**, only four steps are required to reach aplykurodinone-1 (**1**).



Scheme 6. Reagents and conditions: a) L-Phe (30 mol%), PPTS (50 mol%), DMSO, 50°C, 2 days, 68%, 91% *ee*. DMSO = dimethyl sulfoxide, PPTS = pyridinium *p*-toluenesulfonate.

With a formal stereoselective approach to **1** in hand, the asymmetric formation of the stereogenic quaternary carbon center of **7** was undertaken (Scheme 6). In accordance with our synthetic plan, the annulation of prochiral compound **6** was carried out by applying the conditions described by Ohshima, Shibasaki, and co-workers.[7q] Hence, **6** was converted to ketone (−)-**7** (68% yield, 2 days) with high enantioselectivity (91% *ee*) in the presence of L-phenylalanine (L-Phe). As an appealing feature of our strategy, a simple and commercially available catalyst is employed to forge the chiral architecture of the aplykurodinone family, thus allowing the first enantioselective approach to **1**.

In summary, an asymmetric and formal synthesis of aplykurodinone-1 (**1**) has been devised combining step economy and simplicity.[17] Overall, 15 steps are required to attain **21** in 4% yield from commercially available reagents (22 steps for the previous racemic approach). The key features of the strategy are 1) the directed and aerobic oxidation of a Hajos–Parrish-type substrate, 2) a chemo- and stereoselective reduction of an enedione, and 3) a controlled epimerization based on vicinal repulsion to enhance existing 1,3-diaxial interactions. We believe that this study opens the way to new strategies for the asymmetric preparation natural products containing the hydrindane framework. Investigations on the scope and limitation of these methodologies and their extensions to other natural products are ongoing.

Received: February 19, 2013
Revised: March 27, 2013
Published online: May 23, 2013

Keywords: epimerization · oxidation · oxygen · quaternary stereocenters · total synthesis

[1] M. Gavagnin, M. Carbone, M. Nappo, E. Mollo, V. Roussis, G. Cimino, *Tetrahedron* **2005**, *61*, 617.
[2] M. J. Ortega, E. Zubía, J. Salvá, *J. Nat. Prod.* **1997**, *60*, 488.
[3] S. Shen, H. Zhu, D. Chen, D. Liu, L. van Ofwegen, P. Proksch, W. Lin, *Tetrahedron Lett.* **2012**, *53*, 5759.
[4] J. A. R. Salvador, J. F. S. Carvalho, M. A. C. Neves, S. M. Silvestre, A. J. Leitao, M. M. C. Silva, M. L. Sá e Melo, *Nat. Prod. Rep.* **2013**, *30*, 324.
[5] Y. Zhang, S. J. Danishefsky, *J. Am. Chem. Soc.* **2010**, *132*, 9567.
[6] Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1973**, *38*, 3239.
[7] For recent applications to total synthesis, see: a) R. A. Murphy, R. Sarpong, *Org. Lett.* **2012**, *14*, 632; b) K.-W. Tsao, C.-Y. Cheng, M. Isobe, *Org. Lett.* **2012**, *14*, 5274; c) D. T. Hog, P. Mayer, D. Trauner, *J. Org. Chem.* **2012**, *77*, 5838; d) L. Trzoss, J. Xu, M. H. Lacoske, W. C. Mobley, E. A. Theodorakis, *Org. Lett.* **2011**, *13*, 4554; e) J. Xu, L. Trzoss, W. K. Chang, E. A. Theodorakis, *Angew. Chem.* **2011**, *123*, 3756; *Angew. Chem. Int. Ed.* **2011**, *50*, 3672; f) K. Michalak, J. Wicha, *J. Org. Chem.* **2011**, *76*, 6906; g) S. Yamashita, K. Iso, K. Kitajima, M. Himuro, M. Hirama, *J. Org. Chem.* **2011**, *76*, 2408; h) M. Qian, D. F. Covey, *Adv. Synth. Catal.* **2010**, *352*, 2057; i) J. L. Frie, C. S. Jeffrey, E. J. Sorensen, *Org. Lett.* **2009**, *11*, 5394; j) Y. Murata, D. Yamashita, K. Kitahara, Y. Minasako, A. Nakazaki, S. Kobayashi, *Angew. Chem.* **2009**, *121*, 1428; *Angew. Chem. Int. Ed.* **2009**, *48*, 1400; k) L. C. Miller, J. M. Ndungu, R. Sarpong, *Angew. Chem.* **2009**, *121*, 2434; *Angew. Chem. Int. Ed.* **2009**, *48*, 2398; l) M. Lee, C. Nieto-Oberhuber, M. D. Shair, *J. Am. Chem. Soc.* **2008**, *130*, 16864; m) O. V. Larionov, E. J. Corey, *J. Am. Chem. Soc.* **2008**, *130*, 2954; n) K. C. Nicolaou, Y.-P. Sun, X.-S. Peng, D. Polet, D. Y.-K. Chen, *Angew. Chem.* **2008**, *120*, 7420; *Angew. Chem. Int. Ed.* **2008**, *47*, 7310; o) B. W. Katona, N. P. Rath, S. Anant, W. F. Stenson, D. F. Covey, *J. Org. Chem.* **2007**, *72*, 9298; p) T. J. Reddy, G. Bordeau, L. Trimble, *Org. Lett.* **2006**, *8*, 5585; q) H. Shigehisa, T. Mizutani, S. Tosaki, T. Ohshima, M. Shibasaki, *Tetrahedron* **2005**, *61*, 5057; r) T. P. Brady, S. H. Kim, K. Wen, C. Kim, E. A. Theodorakis, *Chem. Eur. J.* **2005**, *11*, 7175; s) R. Iyengar, K. Schildknegt, M. Morton, J. Aube, *J. Org. Chem.* **2005**, *70*, 10645; t) T. P. Brady, S. H. Kim, K. Wen, E. A. Theodorakis, *Angew. Chem.* **2004**, *116*, 757; *Angew. Chem. Int. Ed.* **2004**, *43*, 739.
[8] a) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363; b) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402; *Angew. Chem. Int. Ed.* **1998**, *37*, 388, c) H. Kotsuki, N. Sasakura in *New and Future Developments in Catalysis — Catalysis for Remediation and Environmental Concerns* (Ed: S. Suib), Elsevier, **2013**, in press..
[9] See the Supporting Information for details.
[10] Only **11** and **8** were observed during the reaction, see the Supporting Information for details.
[11] For some reports on the γ-oxidation of α,β-unsaturated ketones, see: a) N. Huwyler, E. M. Carreira, *Angew. Chem.* **2012**, *124*, 13243; *Angew. Chem. Int. Ed.* **2012**, *51*, 13066; b) B. Defaut, T. B. Parsons, N. Spencer, L. Male, B. M. Kariuki, R. S. Grainger, *Org. Biomol. Chem.* **2012**, *10*, 4926; c) G.-Q. Tian, J. Yang, K. Rosa-Perez, *Org. Lett.* **2010**, *12*, 5072; d) T. K. M. Shing, Y.-Y. Yeung, P. L. Su, *Org. Lett.* **2006**, *8*, 3149; e) S. Díaz, A. González, B. Bradshaw, J. Cuesta, J. Bonjoch, *J. Org. Chem.* **2005**, *70*, 3749; f) A. J. Catino, R. E. Forslund, M. P. Doyle, *J. Am. Chem. Soc.* **2004**, *126*, 13622; g) R. Iyengar, K. Schildknegt, J. Aubé, *Org. Lett.* **2000**, *2*, 1625; h) G. Stork, E. W. Logush, *J. Am. Chem. Soc.* **1980**, *102*, 1219; see also Ref. [7s]; for enzymatic γ-oxidation, see: i) V. Goubaud, A. Hammoumi, J. P. Girault, G. Revial, J. d'Angelo, R. Azerad, *Tetrahedron: Asymmetry* **1995**, *6*, 2811.
[12] Catalysts such as $[Rh_2(cap)_4]$ (cap = caprolactamate) or $Mn(OAc)_3$ in combination with *t*BuOOH led to **8** in 32% and 38%, respectively (see the Supporting Information for details).
[13] For pioneering studies on the aerobic γ-oxidation of γ,δ-unsaturated ketones promoted by copper(II)–amine complexes, see: a) H. C. Volger, W. Brackman, *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 579; b) H. C. Volger, W. Brackman, J. W. F. M. Lemmers, *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 1203.
[14] The relative configuration of **14** and **9** was established by 2D NMR analyses after synthetic transformations (see the Supporting Information for details).
[15] For the preparation of the side chain, see: a) P. Le Ménez, V. Fargeas, J. Poisson, J. Ardisson, J. Y. Lallemand, A. Pancrazi, *Tetrahedron Lett.* **1994**, *35*, 7767; b) D. F. Taber, T. E. Christos, *J. Am. Chem. Soc.* **1999**, *121*, 5589. The 1,4 addition was carried out according to a slightly modified version of the procedure reported in Ref. [5].
[16] T. M. Hansen, G. J. Florence, P. Lugo-Mas, J. Chen, J. N. Abrams, C. J. Forsyth, *Tetrahedron Lett.* **2003**, *44*, 57.
[17] T. Newhouse, P. S. Baran, R. W. Hoffmann, *Chem. Soc. Rev.* **2009**, *38*, 3010.

