ORGANIC LETTERS

2008
Vol. 10, No. 9
1787−1790

Enantioselective Synthesis of Iridal, the Parent Molecule of the Iridal Triterpenoid Class

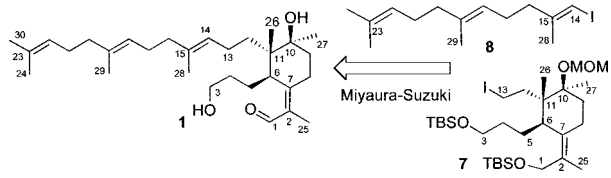
Andrei Corbu, Maurizio Aquino, T. V. Pratap, Pascal Retailleau, and Siméon Arseniyadis*

Institut de Chimie des Substances Naturelles, CNRS, F-91198 Gif-sur-Yvette, France

simeon.arseniyadis@icsn.cnrs-gif.fr

Received March 10, 2008

ABSTRACT



The monocyclic triterpene iridal 1 (parent molecule) is synthesized by an approach that allows access for several representatives of the iridal family as well as diversely substituted analogues. The success of the proposed synthetic plan depends upon the effortless stereoselective establishment of the *trans* C10/C11 dimethyl relationship in B-ring moiety 7 using a domino-based methodology and the higly efficient Miyaura−Suzuki type sp^3-sp^2 segment coupling 7 and 8, respectively.

The iridals comprise several families of naturally occurring mono- or bicyclic A-seco triterpenes that have in common a central B-ring nucleus bearing adjacent quaternary carbons, a three carbon side chain, and a formylolefin. While the monocyclic iridal parent molecule **1**[1] contains a homofarnesyl chain at C11, some members are hydroxylated at C16, C17, C21, or C23 and epoxidized or dihydroxylated at $\Delta^{22,23}$, and others are bicyclic **2**, **3**, or spirocyclic **4** (Figure 1). Discovered by Marner et al.,[2] the title compounds show a broad range of biological activities including antitumor, MDR reversal,[3] antiplasmodial,[4] membrane reinforcing,[5] and protein kinase C activation.[6] The challenging structures, fascinating biosynthetic origins, and wide-ranging biological activities of these terpenoids have, curiously, not stimulated synthetic efforts.

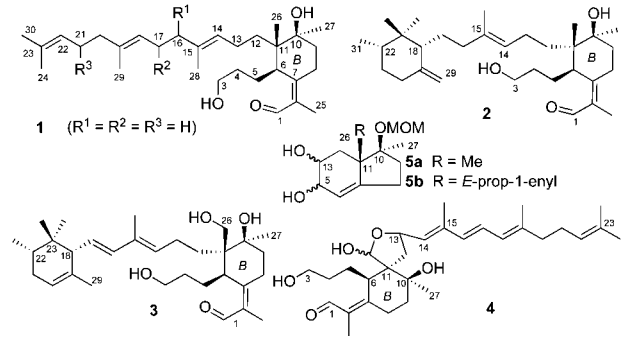


Figure 1. Iridal triterpenoids accessible from hydrindene-diols **5a** and **5b**.

(1) Krick, W.; Marner, F.-J.; Jaenicke, L. *Z. Naturforsch.* **1983**, *C 38*, 179–184.

(2) (a) Marner, F.-J.; Krick, W.; Gellrich, B.; Jaenicke, L.; Winter, W. *J. Org. Chem.* **1982**, *47*, 2531–2538. (b) Marner, F.-J. *Curr. Org. Chem.* **1997**, *1*, 153–186. (c) Lamshoft, M.; Schmickler, H.; Marner, F.-J. *Eur. J. Org. Chem.* **2003**, 727−733.

(3) Bonfils, J.-P.; Pinguet, F.; Culine, S.; Sauvaire, Y. *Planta Med.* **2001**, *67*, 79–81.

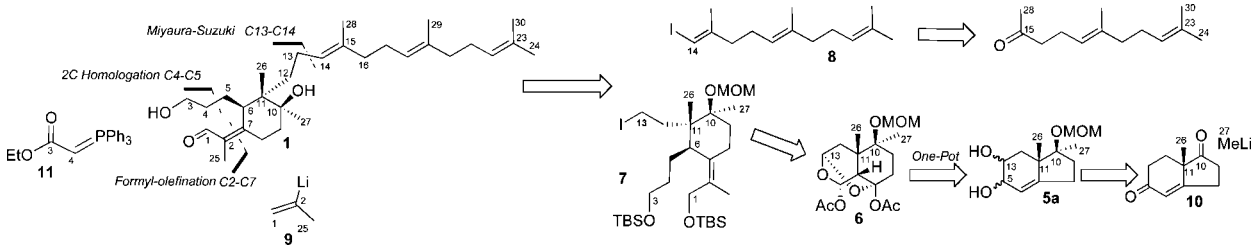
(4) Benoit-Vical, F.; Imbert, C.; Bonfils, J.-P.; Sauvaire, Y. *Phytochemistry* **2003**, *62*, 747–751.

(5) Littek, A.; Marner, F.-J. *Helv. Chim. Acta.* **1991**, *74*, 2035–2042.

(6) (a) Shao, L.; Lewin, N. E.; Lorenzo, P. S.; Hu, Z.; Enyedy, I. J.; Garfield, S. H.; Stone, J. C.; Marner, F.-J.; Blumberg, P. M.; Wang, S. *J. Med. Chem.* **2001**, *44*, 3872–3880. (b) Wender, P. A.; Kogen, H.; Lee, H. Y.; Munger, J. D.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8957–8958. (c) Wender, P. A.; Koehler, K. F.; Sharkey, N. A.; Dell'Aquila, M. L.; Blumberg, P. M. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 4214–4218.

10.1021/ol8005425 CCC: $40.75
Published on Web 04/09/2008

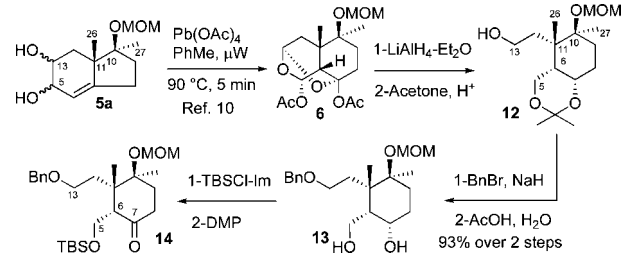
Scheme 1. Retrosynthetic Analysis Based on a Domino Reaction (**5a** → **6**) and an sp^3-sp^2 Miyaura−Suzuki Coupling (**7** + **8**) as Key Construction Steps



Indeed, there have been only a few attempts to develop efficient synthetic routes in spite of the broad range of biological activities displayed by the iridals.[7] Inspired by the potential therapeutic applications of iridals, we have initiated a program directed toward the development of enantioselective methods for their synthesis. Crucial problems to be addressed in this connection are methods for constructing the central B-ring,[8] offering linking possibilities and stereochemical control at the quaternary centers. An experimentally appealing means for the synthesis of the central B-ring involves the approach that we reported in our previous paper, where $Pb(OAc)_4$-mediated domino[9] reactions of unsaturated 1,2-diols of type **5** (Figure 1) provided access to the triterpene core of iridals.[10] Our attention focused initially on iridals **1** and **2**, the parent molecule, and γ-irigermanal, respectively. For this to be achieved, optically homogeneous unsaturated bicyclic diol **5a** would serve as a B-ring precursor, while iripallidal **3** and spiroidal **4** would require the domino substrate diol **5b**. Although this approach does not afford an opportunity for a direct control of the C6 stereochemistry, access would be gained in later steps.

The retrosynthetic scheme to which we were attracted involved disconnection of the strategic bonds as indicated in Scheme 1. We subdivided the task into its four obvious components: the cyclohexane **7**, the 15-nor farnesyl chain **8**, the two-carbon homologation source **11**, and the formyl-olefination source **9**. Thus, geranylacetone-derived *E*-vinyl iodide **8**, carboethoxy ylide **11**, and propenyllithium **9** together with the hydrindene-diol **5a**, assembled from (*S*)-(+)-Hajos-Parrish ketone **10**, would provide the entire iridal triterpene backbone. We describe in this contribution the total synthesis of iridal parent molecule **1**, which also enables acquisition of other iridals, in the correct stereochemical series. The groundwork of this approach has been to prepare a stereodefined cyclohexane precursor allowing for side chain elaboration at C5 (two-carbon homologation), C7 (formyl-olefination), and C13 ("farnesylation"). This requires the stereochemistry at C10, C11 to be established in the central B-ring building block and orthogonal protection of the different hydroxyl groups. The required unsaturated diol **5a** provided a convenient route to the complex oxygen heterocycle **6** possessing functionality and absolute configuration that are appropriate for the central B-ring elaboration.[11] The domino product **6** obtained in a large scale (20−50 g batches) not only provides the two adjacent quaternary stereocenters but also offers handles for the attachment of the missing carbons. The sequence began with the three-step conversion of key intermediate **5a** into the tetrasubstituted cyclohexane **12** using our published procedures.[10]

Scheme 2. Preparation of the C6-epi B-Ring Precursor



Starting from isopropylidene alcohol **12**, benzyl protection at C13, acetonide cleavage, subsequent selective protection of the resulting diol **13** as its corresponding *tert*-butyldimethylsilylether, and finally Dess-Martin oxidation provided **14** in 80% isolated yield. The TBS-protected aldol **14** requires a two-carbon homologation and further necessitates the appropriate adjustment of C6 stereochemistry (an inversion of configuration is required). Fluoride-mediated desilylation caused partial crotonization of the aldol giving rise to the enone **15**, along with C6(*S*) **16** and C6(*R*) **17** aldols. Instead, by effecting the deprotection at 0 °C, aldols **16** and **17** could be obtained as the major constituents (2:1 ratio of **16**:**17**, nearly 80% combined yield) of a three-component

(7) Marner, F. J.; Kasel, T. *J. Nat. Prod.* **1995**, *58*, 319–323.

(8) The constant structural motif in the iridal series is the central six-membered B-ring, incorporating two adjacent quaternary centers at C10, C11. The same ring system, albeit with different locations of unsaturation and oxygen functionality, is found in a great number of related molecules.

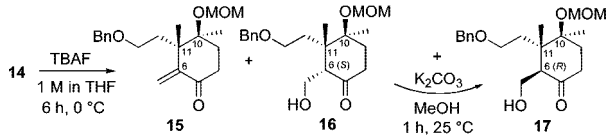
(9) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. (b) Tietze, L. F.; Haunert, F. In *Stimulating Concepts in Chemistry*; Shibasaki, M., Stoddart, J. F., Vogtle, F., Eds.; Wiley-VCH: Weinheim, Germany, 2000; pp 39−64. (c) *Domino Reactions In Organic Synthesis.*; Tietze, L. F., Brasche, G., Gericke, K. M., Eds.; Wiley-VCH: Weinheim, Germany, 2006; ISBN: 3-527-29060-5.

(10) Corbu, A.; Gauron, G.; Castro, J. M.; Dakir, M.; Arseniyadis, S. *Org. Lett.* **2007**, *9*, 4745–4748.

(11) Both quaternary stereogenic centers are obtained as required; no stereoisomer formation was detected.

mixture where enone **15** accounted for around 15%. Considerable experimentation was needed to optimize the selectivity of this reaction, and the best results are summarized in Scheme 3.

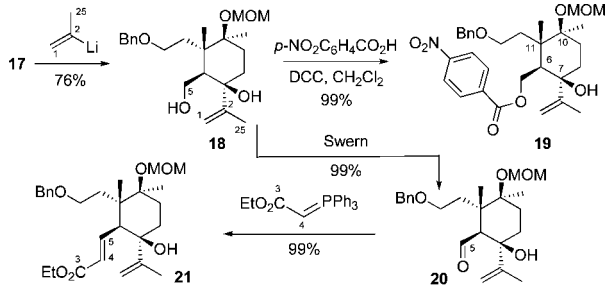
Scheme 3. Installation of the Last Stereogenic Center (C6)



Thus, careful desilylation followed by equilibration of the resulting C6(*S*)/C6(*R*) aldol mixture with K_2CO_3 in methanol at room temperature gave a three-component mixture containing **16** (43%), **17** (30%), and **15** (16%). A final 1.4:1 mixture of C6(*S*) **16**/C6(*R*) **17** was formed upon resubjection to equilibration, and the ratio did not change after prolonged stirring. The efficiency of this process was improved by recycling the C6-α aldol after chromatographic separation. The aldol product **17** carries the whole stereochemical imprint of the subgoal system **7**.

The stage was at hand to put into practice the strategy implied in Scheme 1. With the aim of introducing the C1, C2, C25 unit as a potential formylolefin, **17** was reacted with (2-propenyl)lithium to yield the corresponding carbinol **18** (76% based on recovered **17**, no trace of the C7 epimer could be detected). Swern oxidation of the free alcohol at C5 gave the desired aldehyde **20**, which was poised for a C5−C4 bond-forming step for the completion of the C5−C3 side chain. This was achieved by a Wittig olefination, which furnished the α,*β*-unsaturated ester **21**. The stereochemistry of C6(*R*) in the original aldol **16** follows from the X-ray structure determination of the key domino product **6**,[10] while the C6(*S*) configuration for the epimeric aldol **17** was confirmed by an X-ray diffraction analysis of the crystalline *para*-nitrobenzoate derivative **19** (Scheme 4) (Figure 2) derived from its corresponding carbinol **18**.

Scheme 4. Addition of the Missing Carbons



Another concern in this scheme was the regioselective placement of the C1, C25 carbons during the formyl olefination. Dauben−Michno oxidative rearrangement[12] of **21** provided the transposed enones **22***EZ* and **22***EE* in a 6.4:1 ratio and 52% combined yield (over two steps). The major compound (**22***EZ*) contains all the necessary stereochemical information to reach the goal system **1**, while its geometrical isomer (at the α,*β*-unsaturated aldehyde moiety) **22***EE* could be used for the synthesis of natural iridals with a $\Delta^{7,2}$ *E*-geometry. The requisite B-ring building block, **7***Z*, together with its geometrical isomer, **7***E*,[13] was readily accessed carrying out in parallel the sequence described in Scheme 5. Thus, elaboration of **22** to the requisite substrate **7** began with the protection of the unstable aldehyde function as a TBS-ether **23** by a Luche reduction and a subsequent silylation. Selective reduction of the acrylate moiety then in **23** leaving intact the $\Delta^{7,2}$ olefin was achieved using the Mg/MeOH reduction.[14] Subsequent reduction and MOM protection of the resulting alcohol at C3 afforded **24***Z* uneventfully. For **24***E*, we decided to proceed via a C3-OTBS protection to explore an alternative deprotection/selective oxidation path and check function compatibility for the postcoupling operations (Scheme 6). Following debenzylation, the corresponding C13 alcohols were converted to the target **7***Z* and **7***E* iodides. The geometrically pure *E*-vinyl iodide **8** which would serve as a farnesyl chain precursor was prepared from geranyl acetone in two straightforward steps, employing published procedures.[15]

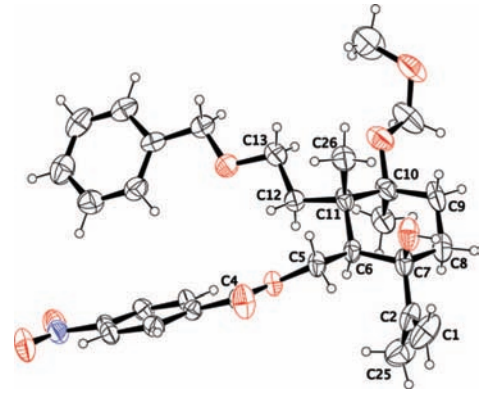


Figure 2. ORTEP drawing of *p*-nitrobenzoyl ester **19**.

Thus, conversion of geranyl acetone into the required terminal alkyne followed by a sequential carboalumination−iodinolysis[16] allowed for the preparation of **8** in quantity. To accomplish the key segment coupling of **7** and **8**, we

(12) (a) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 643–685. (b) Babler, J. H.; Olsen, D. O.; Arnold, W. H. *J. Org. Chem.* **1974**, *39*, 1656–1658.

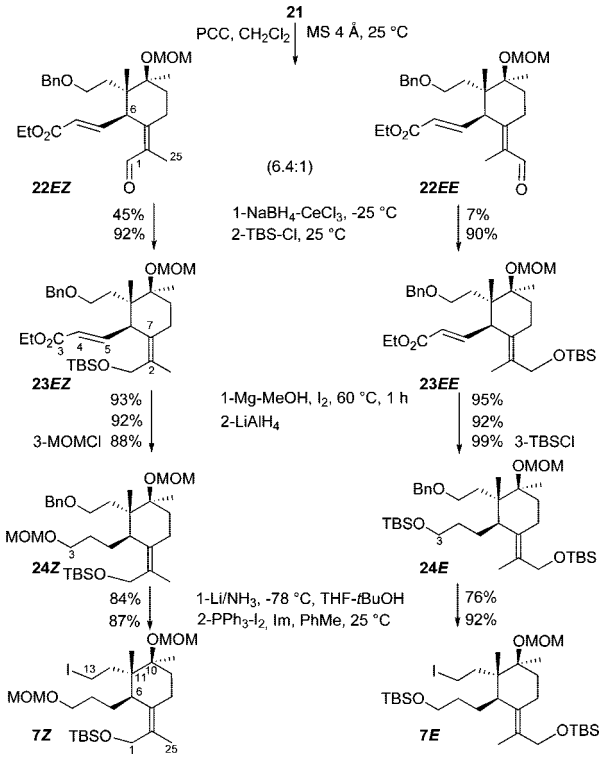
(13) (a) Takahashi, K.; Suzuki, S.; Hano, Y.; Nomura, T. *Biol. Pharm. Bull.* **2002**, *25*, 432–436. (b) Fang, R.; Houghton, P. J.; Luo, C.; Hylands, P. J. *Phytochemistry* **2007**, *68*, 1242–1247.

(14) For the original procedure (reduction of acrylonitriles) see: Profitt, J. A.; Watt, D. S.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 127. Adapted to α,*β*,-unsaturated esters by: Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G. *Tetrahedron Lett.* **1987**, *28*, 5287−5290.

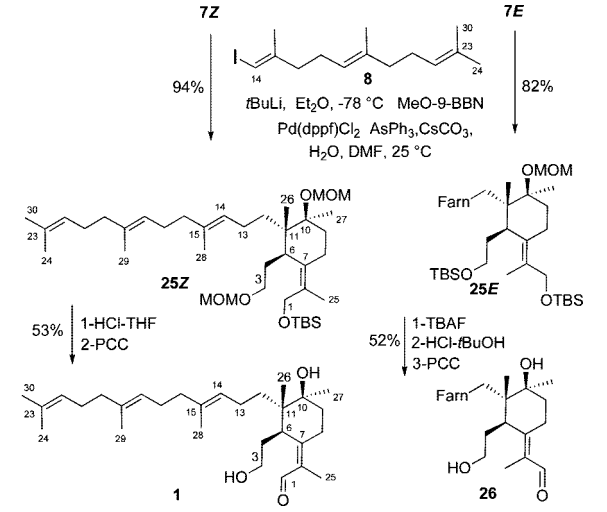
(15) Negishi, E.; King, A. O.; Klima, W. L. *J. Org. Chem.* **1980**, *45*, 2526–2528.

(16) Negishi, E.; Takahashi, T. *Synthesis* **1988**1−19, and references cited therein.

Scheme 5. Preparation of the Central B-Ring Segments **7***Z*/*E*



Scheme 6. Completion of the Synthesis of Iridal **1**



[a] Farn stands for the C13-C30 farnesyl chain

opted to employ the Marshall protocol[17] for a Suzuki−Miyaura reaction,[18] which produced the desired coupling products **25** in good yield (Scheme 6). With the whole iridal triterpene core **25** in hand, conversion to iridal only requires deprotection (C1, C3, C10) and adjustment of the oxidation state at C1. Conversion of **25***Z* into the target iridal **1** was readily accomplished in two steps. Simultaneous acidic deprotection of all protecting groups followed by a PCC-mediated selective allylic oxidation, afforded in 53% isolated yield, synthetically derived (+)-iridal **1** ($[\alpha]_D^{20}$ 33.3°, lit. 34.4°) was spectroscopically indistinguishable from the naturally derived substance.[1] The geometrical isomer[19] **26** was synthesized from the C3-OTBS protected **25***E* starting with TBS removal at C3 and C25. Subsequently, the C10-MOM group was cleaved with HCl-THF to provide the corresponding triol, whose PCC oxidation as above served to provide aldehyde **26** in 52% overall yield. It should be pointed out that the latter was also formed by leaving **1** in the NMR tube ($CDCl_3$) for eight days (**1**/**26** ratio found to be 1:0.3).

In summary, the feasibility of using a domino-based central B-ring formation and Pd(0)-catalyzed sp^3-sp^2 segment coupling as key reaction steps for the enantioselective construction of the iridal backbone has been demonstrated. Application of this methodology to the synthesis of congeners from this class of natural products is under way.

Acknowledgment. The authors wish to thank Professor Jean-Yves Lallemand (Institut de Chimie des Substances Naturelles, CNRS, Gif-sur-Yvette) for his kind interest and constant encouragement.

Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8005425

(17) Marshall, J.; Schaaf, G. M. *J. Org. Chem.* **2003**, *68*, 7428–7432.

(18) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. Chemler, S. R.; Trauner, D.; Danishevsky, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544–4568.

(19) Numerous iridals containing a $\Delta^{7,2}$ *E* double bond are known: Takahashi, K.; Suzuki, S.; Hano, Y.; Nomura, T. *Biol. Pharm. Bull.* **2002**, *25*, 432–436.