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A Domino-Based Approach toward Stereodefined Heavily Functionalized Cyclohexanes: Synthesis of Iridal's Core Structure

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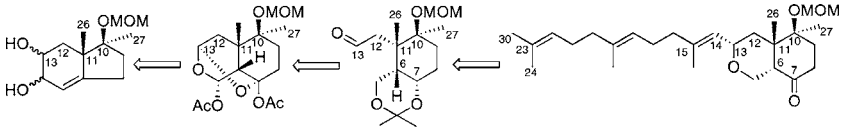
ABSTRACT



A stereoselective synthesis of heavily functionalized six-membered ring subunits, which possess functionality at sites appropriate for further elaboration, is described. The cyclopentanone moiety of hydrindenediol is required to achieve total facial selectivity during the pre-domino installation of the second quaternary center, while oxidative cleavage is responsible for the ring-expanding rearrangement. A microwave-assisted version of the key domino transformation and a test of concept approach toward the iridal core structure are also presented.

Discovered by Marner et al., iridals are products of an unusual squalene metabolism in Sword Lilies (*Iridaceae*).[1] Despite their relatively simple chemical structures, they show an important biological activity pattern similar to that of doxorubicin and taxol[2] for iridal **I** and γ-irigermanal **II**, or to that of phorbol esters[3] for iripallidal **III** and spiroiridal (NSC 631941) **IV** (Figure 1). There is experimental evidence that the iridals serve the plants as membrane constituents and protect the tissue against oxidative damage and other noxious influences.[4] Several members of this family have been isolated by Marner's group, and an excellent review article was reported.[5]

Central to each of these A-*seco* triterpenes is a cyclohexane moiety (B-ring), which incorporates vicinal quaternary methyl groups (C10, C11) *trans* to each other. Over the last 10 years, we developed a domino protocol[6] for the transformation of bicyclic unsaturated vicinal diols into significantly more complex domino products by a lead tetraacetate (LTA)-induced oxidative cleavage.[7] A key feature of this transformation is a ring expansion generating a complex

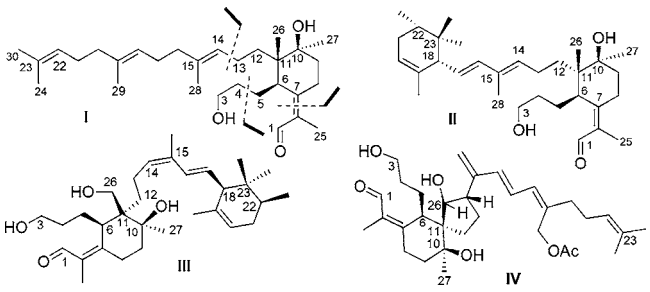


Figure 1. Iridal triterpenoids and strategic bond disconnection.

(1) (a) Marner, F.-J.; Krick, W.; Gellrich, B.; Jaenicke, L.; Winter, W. *J. Org. Chem.* **1982**, *47*, 2531−2538. (b) Jaenicke, L.; Marner, F. *Pure Appl. Chem.* **1990**, *62*, 1365−1368. (c) Marner, F.-J.; Longerich, I. *Liebigs Ann. Chem.* **1992**, 269−272. (d) Effers, K.; Scholz, B.; Nickel, C.; Hanisch, B.; Marner, F.-J. *Eur. J. Org. Chem.* **1999**, 2793−2797. (e) Lamshoft, M.; Schmickler, H.; Marner, F.-J. *Eur. J. Org. Chem.* **2003**, 727−733.

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

(3) (a) 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. (b) 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. (c) Wender, P. A.; Cribbs, C. M.; Koehler, K. G.; Sharkey, N. A.; Herald, C. L.; Kamano, Y.; Pettit, G. R.; Blumberg, P. M. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 7197−7201. (d) Tanaka, M.; Irie, K.; Nakagawa, Y.; Nakamura, Y.; Ohigashi, H.; Wender, P. A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 719−722. (e) 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.

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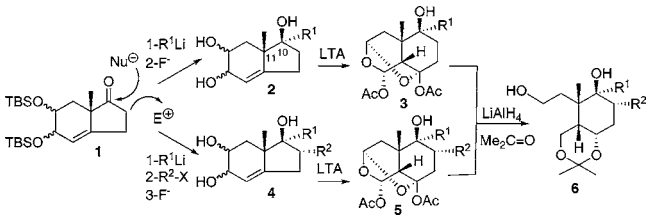
oxygen heterocycle, which incorporates chemodifferentiable sites that can be used as either electrophiles or nucleophiles in subsequent reactions. Stimulated by the potential therapeutic applications of iridals, we have initiated a program directed toward the development of an enantioselective method for their synthesis. To date, to the best of our knowledge, the only synthetic endeavor in this field is the one reported by Marner et al. on a biomimetic synthesis of an iridal analogue, which lacks the C10 hydroxyl group while the C10 methyl group (Me-27) has the opposite configuration.[8] We therefore prepared the TBS-protected Hajos−Parrish ketone derivative **1**,[9] which served as a starting material for targeted substrates of type **2** and **4**, precursors for the manufacture of heavily substituted cyclohexanes with four and five chiral centers of type **6** ($R^2 = H$ and $R^2 \neq H$, respectively, Scheme 1). This was achieved upon stereoselective nucleophilic addition on **1**, through variation of the nucleophile's nature and the quenching mode, as shown in Scheme 1. Submitting compounds of type **2** and **4** to the standard domino conditions would give the expected ring-expanded domino products of type **3** or **5**, en route to 1,2,3,4-tetra- and 1,2,3,4,5-pentasubstituted stereodefined cyclohexanes of type **6**.

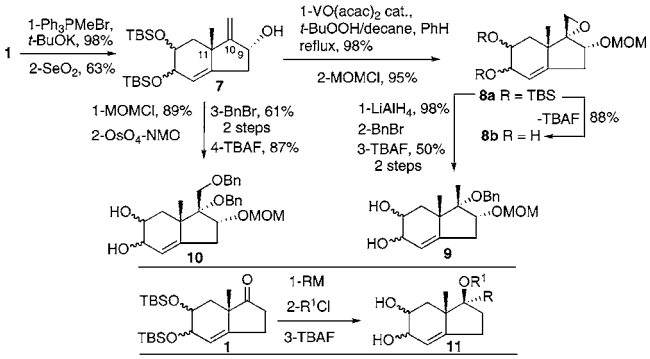
Scheme 1. Construction of the Domino Precursors and Access to Heavily Substituted Type **6** Cyclohexanes



The starting diols **2** and **4** were prepared from **1**, by sequential treatment with methyllithium, then quenching with a suitable electrophile (water for **2**, alkyl halide for **4**) since considerable enolization could be observed. Thus, when the bis-TBS-protected unsaturated bicyclic diol **1** was reacted with methyllithium in THF at −78 °C, a mixture of the required methyl carbinol **2** ($R^1 = Me$, 50%) along with unreacted starting material (45%) was obtained. Upon quenching of the above reaction with freshly distilled methyl iodide (filtered on basic alumina), the α-methyl ketone of **1** was obtained along with the methylcarbinol **2** ($R^1 = Me$). Proceeding as above by quenching with freshly distilled allylbromide, α-allyl ketone **1** was obtained along with the methyl carbinol. These two products can also be accessed directly via LDA−THF then quenching with either MeI or allylbromide.

The conformational bias of the hydrindenone system in **1** allows controlled placement of functional groups in the resulting ring-expanded domino products. Hence, by using the appropriate sequencing of the steps, the methyl groups at C10 and C11 quaternary centers (iridal numbering) can be either *trans* (**2**, **4**, **11**) or *cis* (**9**) to each other (Scheme 2).

Scheme 2. Variations at C10 Stereochemistry



11a R = Allyl, R^1 = Ac — 1) AllylMgBr, THF, -78 °C, 95% 2) Ac_2O, Py, DMAP, 25 °C, 83% 3) TBAF, THF, 25 °C, 88%

11b R = Propynyl, R^1 = H — 1) propyne, *n*-BuLi, HMPA, THF, -78 °C to 25 °C 2) H_2O, 82% 3) TBAF, THF, 25 °C, 78%

11c R = Propynyl, R^1 = MOM — 1) propyne, *n*-BuLi, HMPA, THF, -78 °C to 25 °C 2) MOMCl, iPr_2EtN, DCM 3) TBAF, THF, 25 °C, 82% 2 steps

11d R = $\equiv(CH_2)_2OBn$ R^1 = H — 1) 4-benzyloxy-1-butyne, *n*-BuLi, THF-HMPA, -78 °C 2) H_2O, 87% 3) TBAF, THF, 25 °C, 70%

11e R = $MOMCH_2$, R^1 = H — 1)*n*-BuLi, Bu_3SnCH_2OMOM, THF, -78 °C, 81%

11f R = $MOMCH_2$, R^1 = TMS — 2) TMSOTf, collidine, PhMe, -30 °C, 75%

Starting from **1**, a Wittig olefination followed by an allylic oxidation afforded **7** thus introducing a new control element at C9 for a hydroxyl-directed epoxidation, which offers the potential to control the C10 quaternary center. A Sharpless procedure[10] allowed the stereospecific introduction of the epoxide functionality in **8**. Protection of the secondary hydroxyl group as its MOM ether afforded **8a** which, upon desilylation, furnished the substrate diol **8b**. Reductive epoxide opening of **8a** followed by benzyl protection and finally desilylation as above furnished diol **9**. On the other hand, osmylation of MOM-protected **7** followed by benzyl protection and subsequent desilylation afforded the desired diol **10**. Finally, six more variously substituted (R, R^1) substrate diols were prepared straightforwardly as follows. Upon subjection of **1** to allyl Grignard and subsequent

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(5) Marner, F.-J. *Curr. Org. Chem.* **1997**, *1*, 153−186.
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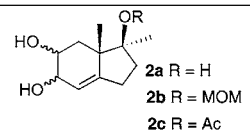
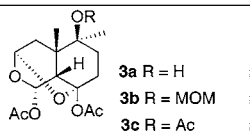
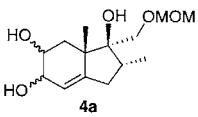
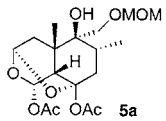
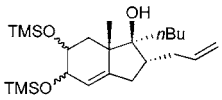
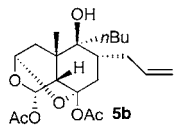
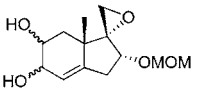
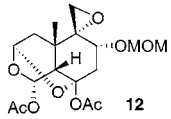
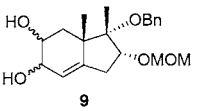
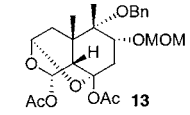
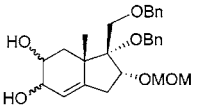
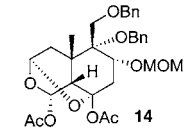
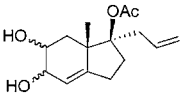
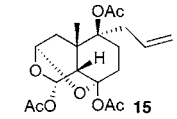
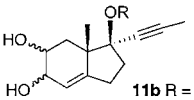
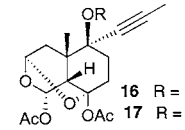
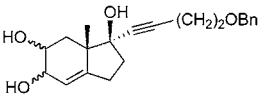
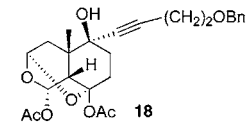
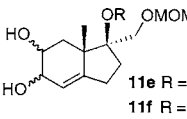
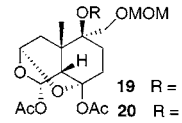
(7) (a) Finet, L.; Candela Lena, J. I.; Kaoudi, T.; Birlirakis, N.; Arseniyadis, S. *Chem.−Eur. J.* **2003**, *9*, 3813−3820. (b) Öztürk, C.; Topal, K.; Aviyente, V.; Tüzün, N.; Sanchez, E.; Arseniyadis, S. *J. Org. Chem.* **2005**, *70*, 7080−7086. (c) Candela Lena, J. I.; Sánchez Fernández, E.; Ramani, A.; Birlirakis, N.; Barrero, A. F.; Arseniyadis, S. *Eur. J. Org. Chem.* **2005**, 683−700. (d) Safir, I.; Castellote, I.; Porcel, S.; Kaoudi, T.; Birlirakis, N.; Toupet, L.; Arseniyadis, S. *Chem.−Eur. J.* **2006**, *12*, 7337−7344.
(8) Marner, F.-J.; Kasel, T. *J. Nat. Prod.* **1995**, *58*, 319−323.
(9) (a) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1973**, *38*, 3239−3243. (b) Hajos, Z. G.; Parrish, D. R. W. German Patent 2,102,623; Hoffmann-La Roche, July 29, 1971; *Chem. Abstr.* **1971**, *75*, 129414r. (c) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496−497. See Supporting Information for experimental details.
(10) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136−6137.

acetylation, **11a** was obtained as a single product. Reaction of **1** with propynyllithium afforded the bis-TBS-protected diol, which by direct desilylation afforded **11b** and, upon initial MOM protection and subsequent desilylation, yielded the corresponding diol **11c**. Exposure of **1** to an excess of 4-benzyloxybutyn-1-yllithium, followed by desilylation afforded diol **11d**. The reaction between **1** (bis-TMS-protected) and α-alkoxyorganolithium derived from Bu_3SnCH_2OMOM[11] furnished **11e**, which in turn was TMS-protected at the C10 position. It is noteworthy that there was no need for desilylation in this case, as the domino reaction in AcOH works on the TMS-protected diols.[7d]

Each substrate diol thus prepared was then reacted with 2.4 equiv of $Pb(OAc)_4$ in toluene (or several other solvents)[12] as indicated in Table 1, and the corresponding complex oxygen heterocycles (entries 1−10) were isolated as single domino products. In our initial studies, room temperature was preferred to heating[13] since at elevated temperatures the reagent would react with unsaturated groups around the diol framework.[14] In all cases investigated, the oxidative cleavage was re-examined under microwave heating,[15] which was found to be more advantageous compared to conventional heating. Indeed, while olefins are inert to $Pb(OAc)_4$ at room temperature and react sluggishly at reflux temperatures, no such complications were observed under microwave heating, even at 100 °C, and the reactions were complete in less than 5 min. The broad scope and efficiency of this ring-expanding rearrangement are illustrated by the results summarized in Table 1 (entries 1−10). The process accommodates free hydroxyl groups (entries 1−3, 8−10), while it tolerates a wide range of solvents and protecting groups. Domino reactions with substrates bearing alkenes (entries 3 and 7), alkynes (entries 8 and 9), epoxides (entry 4), and acetals (entries 1, 2, 4−6, 8, and 10) proceed efficiently to afford the corresponding ring-expanded oxygen heterocycles in good to excellent (51−88%) yields. The domino reaction of **2a** led to the exclusive formation of the ring-expanded domino product **3a** (precursor of a cyclohexane containing *trans*-methyl groups at the C10 and C11 quaternary centers) in 85% yield after 12 h room temperature stirring, and 82% upon 15 min at 80 °C (or 5 min at 90 °C) of microwave irradiation. Moreover, only insignificant differences in the reaction rate were observed in the reactions conducted under microwave activation at either 80 °C (10−15 min) or 90 °C (5 min).

The stereochemistry of **3a** was established by an X-ray crystallographic analysis (see Supporting Information). Methods A (conventional room temperature stirring) and B (microwave irradiation) on all substrate diols resulted solely in formation of the corresponding domino products; we did not isolate any decomposition (or side) product, and this despite significant mass losses.

Table 1. Conventional (A) and Microwave Accelerated (B) Domino Reactions in Six-Membered Ring Construction

entry	substrate	domino product	yield (%) A[a] (B)[b]
1	 **2a** R = H **2b** R = MOM **2c** R = Ac	 **3a** R = H **3b** R = MOM **3c** R = Ac	85 (82) 84 (88) 87 (82)
2	 **4a**	 **5a**	51 (61)
3	 **4b**	 **5b**	52 (56)
4	 **8b**	 **12**	59 (80)
5	 **9**	 **13**	70 (81)
6	 **10**	 **14**	60 (61)
7	 **11a**	 **15**	77 (79)
8	 **11b** R = H **11c** R = MOM	 **16** R = H **17** R = MOM	57 (65) 72 (76)
9	 **11d**	 **18**	80 (69)
10	 **11e** R = H **11f** R = TMS	 **19** R = H **20** R = TMS	80 (72) 72 (76)

[a] Method A (conventional): The substrate (1 mmol), lead tetraacetate (2.4 mmol), and the solvent (5 mL) were stirred at room temperature (TLC monitoring). [b] Method B: A mixture of substrate (1 mmol) and $Pb(OAc)_4$ (2.4 mmol) in 5 mL of toluene was microwaved for 15 min at 80 °C (or 5 min at 90 °C).

With a view toward reaching the iridals, the reaction of unsaturated diol **2b** with LTA (run at room temperature) has been scaled up (20 g or more) and the resulting domino product **3b** (84% isolated yield) has been used as a key intermediate in the natural product synthesis (Scheme 3). A

(11) Danheiser, R. L.; Romines, K. R.; Koyama, H.; Gee, S. F.; Johnson, C. R.; Medich, J. R. *Org. Synth.* **1992**, *71*, 133−139.

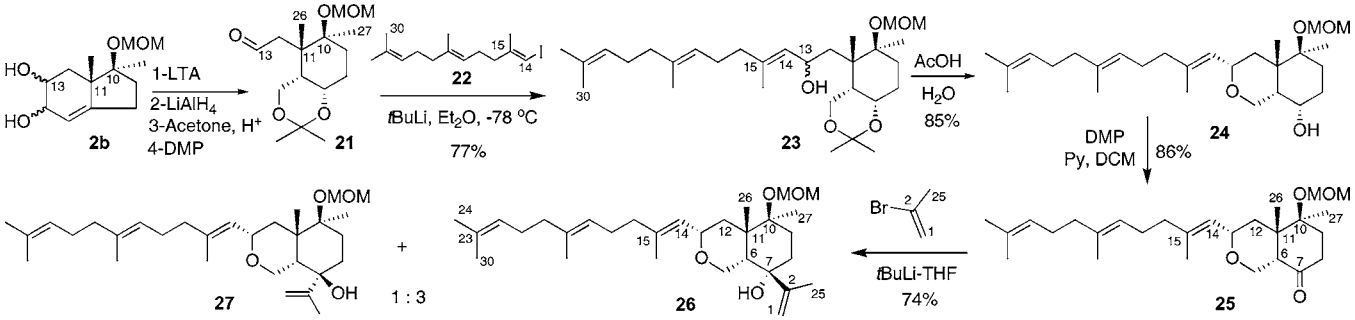
(12) Sesenoglu, Ö.; Candela Lena, J. I.; Altinel, E.; Birlirakis, N.; Arseniyadis, S. *Tetrahedron: Asymmetry* **2005**, *16*, 995−1015.

(13) Conventional heating of the reaction mixture in a normal reflux apparatus gave mixed results (depending on the functionalities present in the substrate) with a significant reduction in the isolated yields.

(14) Criegee, R. In *Oxidation in Organic Chemistry*; Wiberg, K. B., Ed.; Academic Press: New York, 1965; Part A, p 277.

(15) For reviews on the use of microwaves in organic synthesis, see: (a) Loupy, A.; Petit, J.; Hamelin, F.; Texier-Boullet, F.; Jacquault, P.; Mathé, D. *Synthesis* **1998**, 1213−1234. (b) de la Hoz, A.; Diaz-Ortis, A.; Moreno, A.; Langa, F. *Eur. J. Org. Chem.* **2000**, 3659−3673. (c) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283.

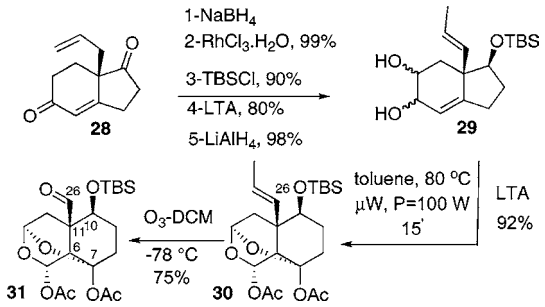
Scheme 3. Synthetic Path toward Iridal's Triterpene Core



convergent enantioselective approach to the basic iridal skeleton, involving the aldehyde **21**, to be used as C13 electrophile via coupling with the geometrically pure (*E*)-vinyl iodide **22** (precursor of the C14-Nu^-) is portrayed in Scheme 3. The further elaborated domino product **21**, generated following procedures used in our previous papers,[16] not only provides the two adjacent quaternary stereocenters but also offers handles for the segment linking (introduction of the C14−C30 unit) and for the attachment of the missing carbons at C6 and C7. The preparation of the requisite vinyliodide **22**, precursor of the C14 nucleophile, from geranylacetone employed standard literature methods.[17] The efficient side chain linking with homologated geranylacetone iodide **22** was carried out uneventfully, affording C13 epimeric alcohols **23**. The latter was converted to the *cis*-fused decalone **25** by successive treatment with AcOH/water[18] and Dess−Martin oxidation. With the aim of introducing the C1, C2, and C25 unit, as a potential formyl olefin, **25** was reacted with (2-propenyl)lithium to yield the carbinols **26** and **27** in a 3:1 ratio, respectively.

In parallel, the bicyclic unsaturated diol **29** was prepared from the known **28**[19] with an eventual view toward a possible synthesis of iripallidal **III** (Figure 1). Hence, subjecting **29** to our domino conditions (Methods A and B) afforded **30**, which upon ozonolysis gave **31**, possessing the requisite functionality in place to be used as a key intermediate for the synthesis of a variety of C26 oxygenated iridal (and spiroiridal) analogues (Scheme 4).

Scheme 4. Studies toward the C26 Oxygenated Systems



In summary, a wide variety of cyclohexanes can be reached efficiently, with complete stereocontrol and good functional group tolerance by the method reported here. The efficient use of microwaves significantly broadens the range of precursors potentially available for assembling heavily substituted six-membered rings. The studies described here, together with our earlier reports, clearly establish the utility of reaction designs that employ domino reactions to synthesize elaborated building blocks.

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

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