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Enantioselective Total Synthesis of 1-*epi*-Pathylactone A[§]

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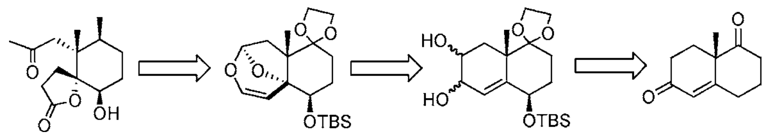
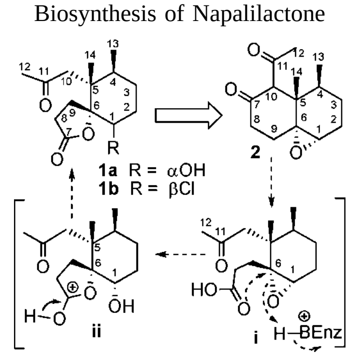
ABSTRACT



The first enantioselective total synthesis of 1-*epi*-pathylactone A, 3, has been accomplished using a $PhI(OAc)_2$-mediated domino reaction as a key step. No diastereomeric separation was required throughout the whole synthetic scheme presented in this paper. Comparison of ^1H and ^{13}C NMR spectral data of the synthetic product with the reported spectral data of natural pathylactone A, coupled with an X-ray crystallographic analysis, led to the conclusion that the C1 configuration in the original paper was erroneously ascribed to (*R*).

In the past few years, we have initiated a program directed toward the synthesis of biologically active natural products accessible by a domino methodology[1] developed in our laboratory. During our investigations of new synthetic routes, we became interested in the "interrupted process" which allows for stereoselective construction of a wide range of products.[2] To demonstrate the effectiveness of this methodology in natural product synthesis, we targeted two norsesquiterpene spirolactones differing only at the C1 substitution (Scheme 1). Pathylactone A **1a**,[3] reported to be a Ca^{2+} antagonist, was isolated from the soft coral *Paralemnalia thyrsoides* (the first example of a γ-spirolactone norsesquiterpenoid from a marine organism), and napalilactone **1b**,[4] a chlorinated sesquiterpenoid, was isolated from *Lemnalia africana* (the first halogenated norsesquiterpenoid from a soft coral). Although no thorough biosynthesis studies have been published, a biosynthetic hypothesis proposed by Scheuer[5] leaves room for both 1α- and 1β-hydroxy configurations for pathylactone A. Taking into account that oxolemnacarnol **2** was isolated by several groups from *Paralemnalia thyrsoides* along with pathylactone A and napalilactone, the aristolene-derived biogenetic pathway proposed by Scheuer could be used as a basis. The proposed hydrolysis of **2** (β-diketone) would lead to **i**, which in turn could undergo an acid-catalyzed epoxide opening to give the spirolactone ring

Scheme 1. Variation of the Scheuer Proposal for the Biosynthesis of Napalilactone



[§] Dedicated to Professor Miguel Yus on the occasion of his 60th birthday.

(1) (a) Tietze, L. F.; Beifuss, U. *Angew. Chem.* **1993**, *32*, 115−136; *Angew. Chem., Int. Ed.* **1993**, *32*, 131−163. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (c) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304−322. (d) Tietze, L. F.; Haunert, F. In *Stimulating Concepts in Chemistry*; Shibasaki, M., Stoddart, J. F., Vogtle, F., Eds.; Wiley-VCH: Weinheim, 2000; p 39−64. Domino Reactions. In *Organic Synthesis*; Tietze, L. F., Brasche, G., Gericke, K. M., Eds.; Wiley-VCH: Weinheim, 2006. ISBN: 3−527-29060-5.

(2) An important experimental improvement was that for the oxidative/pericyclic process $Pb(OAc)_4$ could be replaced by $PhI(OAc)_2$ as the domino promoter, thus decreasing the toxicity of the method. Candela Lena, J. I.; Sánchez Fernández, E.; Ramani, A.; Birlirakis, N.; Barrero, A. F.; Arseniyadis, S. *Eur. J. Org. Chem.* **2005**, 683−700.

(3) Su, J. Y.; Zhong, Y.-L.; Zeng, L.-M. *J. Nat. Prod.* **1993**, *56*, 288−291.

(4) Carney, J. R.; Pharm, A. T.; Yoshida, W. Y.; Scheuer, P. J. *Tetrahedron Lett.* **1992**, *33*, 7115−7118.

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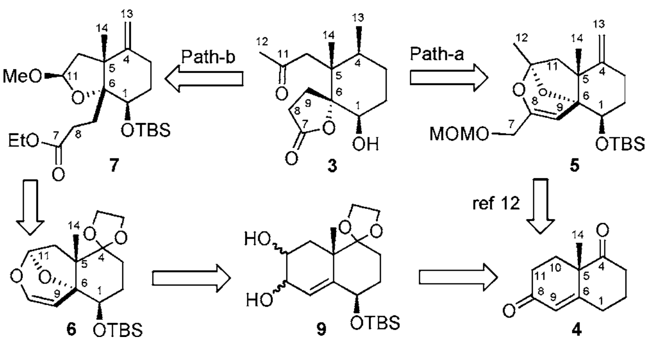
precursor **ii** in its desired configuration (Scheme 1, proposed biogenetic pathway for pathylactone A). The acid-catalyzed opening of transient epoxide **i** would most likely lead to the required C6 stereochemistry via a planar carbocation.

The racemic synthesis of dehalonapalilactone (**1**, R = H, Scheme 1) and hence dehydropathylactone A has been reported by Coelho et al.[6] and Vyvyan et al.,[7] both starting from 2-methylcyclohex-2-enone and using a similar synthetic scheme. Soon after his dehalonapalilactone synthesis, Coelho described a total synthesis of (±)-pathylactone A,[8] which has raised doubts about the spectral assignments of the norsesquiterpene natural product. As a general trend, in these earlier studies the missing carbons were added via an allylation and a subsequent three-carbon homologation, and C12 was added by a Wacker process.

Originally, we considered a dual strategy for the formation of the carbon framework of 1-*epi*-pathylactone A **3** starting from (*S*)-(+)-Wieland−Miescher ketone **4** (Scheme 2).[9] The key transformation in both routes was the $PhI(OAc)_2$-initiated domino reaction to produce the cyclic ene-acetals **5** (path a) and **6** (path b).[10] The missing carbons C7, C12, and C13 would be introduced before the domino step in path a, and their installation would be delayed to a post-domino stage in path b.

Scheme 2. Retrosynthetic Analysis for 1-*epi*-Pathylactone A



The main problem was to set four contiguous stereogenic centers, two of them being quaternary carbons, in a stereoselective fashion. Our initial plan (path a, Scheme 2) called for the preparation of compound **5**[11] which we hoped to convert to pathylactone A and napalilactone by a hydrolytic acetal opening, following a stereoselective reduction of the exocyclic olefin C4−C13. The key aspect of the analysis derived from the idea that the C4 center in **5** could be installed stereoselectively through a catalytic hydrogenation, which would utilize the steric bulk of the bridgehead C14 methyl group to govern the approach of hydrogen from the opposite face thus leading to the formation of a C13 β-methyl group. However, the reduction of the exocyclic olefin gave an unseperable mixture of isomers in a surprisingly low de (ca. 85:15).

The stereochemical difficulties encountered in this approach prompted us to prepare the methylfuranoside **7** via a domino-derived cyclic ene-acetal **6** and to attempt its stereoselective reduction (path b). The success of this scheme would be based on the degree of facial bias that **7** could provide. Also crucial to the achievement of this approach were the efficiency of transthioacetalization and the installation of the last methyl group. The overall conception of a sequence to synthesize norsesquiterpene spirolactones is shown in retrosynthetic format in Scheme 2.

Described herein is the execution of the strategy (path b) culminating in the synthesis of the norsesquiterpene framework **3** starting from (*S*)-(+)-**4**. This approach circumvents the stereoselectivity issue altogether for the four contiguous stereogenic centers.

At the outset of this synthetic endeavor, it was perceptible that the $PhI(OAc)_2$-mediated domino reaction should serve as an effective means for the construction of the substituted cyclohexane portion of the pathylactone A structure. Each of the three stereogenic centers (C1, C5, C6) of the domino product **6** possesses the correct relative configuration for an ultimate synthesis of candidate molecule 1-*epi*-pathylactone A. The required bicyclic unsaturated diol **9** was readily prepared from the known **8**[11] by reduction with excess lithium aluminum hydride ($LiAlH_4$, Et_2O, 0 °C, 30 min, 94%). The cyclic ene-acetal **6** was then accessed with the iodobenzene diacetate mediated domino process ($PhI(OAc)_2$, acetonitrile, 25 °C, 24 h, 72%) which was preferred to $Pb(OAc)_4$, even though the yields were considerably higher using the latter as the domino promoter (1.5 equiv of $Pb(OAc)_4$, PhMe, 25 °C, 90%).

Ozonolytic cleavage of the domino product **6** in methanol was performed at −78 °C, and reaction products isolated by reductive workup (Me_2S) afforded the desired methylfuranoside **10** in high yield (89%, Scheme 3).[12] The latter was obtained as an anomeric mixture (β/α = 10:1), and the major isomer has been characterized as pure, although the anomeric carbon has no long-term significance because it is programmed to be destroyed in later steps. At this point, the missing C7−C8 portion had to be introduced via an HWE olefination.

Horner−Wadsworth−Emmons coupling of aldehyde **10** with commercially available triethyl phosphonoacetate

(5) On the basis of the co-occurrence of pathylactone A and 2-deoxy-12-oxolemnacarnol, Su (ref 4) assumed the latter as a precursor and proposed a biogenetic trans ring opening of the epoxide followed by a simultaneous C7/C10 cleavage and subsequent lactonization, which would give the C1-βOH, but this is not the case.

(6) Diaz, G.; Coehlo, F. *J. Braz. Chem. Soc.* **2001**, *12*, 360−367.

(7) Vyvyan, J. R.; Rubens, C. A.; Halfen, J. A. *Tetrahedron Lett.* **2002**, *43*, 221−224.

(8) Coehlo, F.; Diaz, G. *Tetrahedron* **2002**, *58*, 1647−1656.

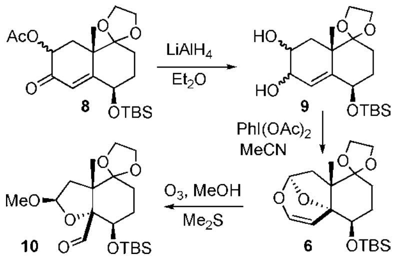
(9) The use of the Wieland−Miescher ketone as a chiral building block in the assembly of complex targets is well established: Wieland, P.; Miescher, K. *Helv. Chim. Acta* **1950**, *33*, 2215−2228. Bushschacher, P.; Fürst, A.; Gutzwiller, J. *Org. Synth. Coll.* **1990**, *7*, 368.

(10) Hypervalent iodine reagents frequently imitate the transformations mediated by Hg^{2+}, Tl^{3+}, Pb^{4+}, and Pd^{2+} but without the toxic and environmental issues: (a) Moriarty, R. M.; Vaid, R. K. *Synthesis* **1990**, 431−447. (b) Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179−1255.

(11) Chanu, A.; Castellote, I.; Commeureuc, A.; Safir, I.; Arseniyadis, S. *Tetrahedron: Asymmetry* **2006**, *17*, 2565−2591.

(12) The methylfuranoside **10** (10:1 β/α anomeric mixture) was separated and characterized from a three-component crude mixture, where **i** and **ii**, the two additional products of the ozonolysis obtained in a ratio of 7.4:1 (6.9% combined yield), could not be obtained pure and thus were characterized as mixtures and then discarded (see Supporting Information).

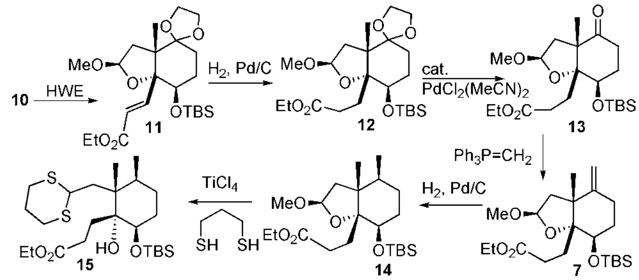
Scheme 3



[$(EtO)_2P(O)CH_2CO_2Et$, NaHMDS, THF, 25 °C, 14 h] proceeded smoothly thus affording the *E*-conjugated ester **11** as the sole geometric isomer in 91% yield. We next addressed the acidic hydrolysis of **11** so as to generate the required olefination precursor **13**. However, attempted ketal deprotection on **11**, under various conditions, proved troublesome.[13] An alternative to the above deketalization was sought that would avoid the problems inherent when deprotecting acetals surrounded with a large number of functional groups. It was subsequently found that ketal deprotection could be bypassed completely by using commercially available Pd/C, presumably containing trace amounts of $PdCl_2$.[14] The conjugated olefin **11** was found to undergo ketal deprotection during the reduction step (H_2, Pd/C, MeOH, 25 °C, 15 h) providing a 77% isolated yield of **13** and thus rendering this upsetting step unnecessary. Furthermore, the latter was obtained along with its corresponding C1 TBS-deprotected derivative (19% yield), which in turn could be easily recycled. Unfortunately, we later discovered that this simultaneous deketalization was random and reproducibility could suffer depending upon the catalyst supplier.[15] With a route to **12** secured, efforts were next directed toward introduction of the C13 methyl group. For this transformation, it was necessary to first deprotect the ketal at C4 and to subsequently install a $\Delta^{4,13}$ double bond.

Clean deprotection, following the reduction step, was finally achieved using the Lipshutz protocol[16] based on palladium^{II} catalysis with acetone as solvent to encourage transketalization. Thus, exposure of **12** to the above conditions (1−5 mol % of bis(acetonitrile)dichloropalladium, 25 °C, 19 h) furnished the free-ketone **13** in 76% isolated yield. Conversion of the latter into the targeted exocyclic olefin **7**, which would be used as the source of the C13 methyl group, proceeded via a Wittig methylenation. This, under standard conditions ($MeP^+Ph_3Br^-$, *t*-BuOK, THF, 25 °C, 3 h), afforded **7** uneventfully (70% isolated yield, Scheme 4).

Scheme 4



At this stage of the synthesis, the exocyclic olefin function of **7** was to be used as a handle for the introduction of the β-methyl group at C13. Molecular models indicated that the C14 angular methyl group offers considerable steric interaction with the β face of the C4,13 olefin. This inherent bias inflicted the facial selectivity, only allowing for reduction by the α face of the ring system (Figure 1).[17]

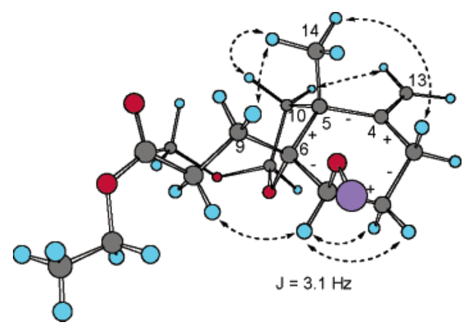


Figure 1.

Following a Wittig olefination to produce the methylidene derivative **7**, reduction to the methyl (H_2, Pd/C, MeOH, 25 °C, 14 h) furnished the desired **14** (76%). The β-configuration (no other isomer was detected) of the newly introduced C13 methyl group was ascertained on the basis of NOE data and *J*-analysis. The complete control of all four contiguous chiral centers of the candidate norsesquiterpene lactone framework was thus achieved at this point. A transthioacetalization of this methyl furanoside with $TiCl_4$−dithiane ($HS(CH_2)_3SH$, $TiCl_4$, −78 to −40 °C, 15 min) provided, as expected, the corresponding dithiane **15** (82% isolated yield).

With the basic carbon skeleton fully assembled and all four stereogenic centers installed, simple function manipulation was required to afford 1-*epi*-pathylactone A **3**. Specifically, the carboethoxy residue needed to be converted to

(13) PPTS, EtOH−H_2O (10:1), reflux, 21 h, 13%; NaI, CH_3CN−H_2O (1:1) $CeCl_3 \cdot 7H_2O$ (91 mg, 0.25 mmol), 4 h, reflux gave a 40% yield of ketal deprotection accompanied by a loss of the C11 methoxy group. HCl−THF (1:1), room temperature, 2 days gave 31% of ketone and 33% of starting ketal, both TBS deprotected.

(14) Preparation of Pd/C: Mozingo, R. *Org. Synth.* **1946**, *26*, 77−82.

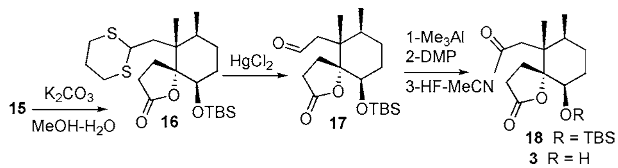
(15) Simultaneous deketalization during reduction proved nonreliable, as it was dependant upon the quality of commercial Pd/C catalyst. Addition of trace amounts of $PdCl_2$ helped deprotection, though we finaly decided to go through the two-step process, for the sake of reproducibility. For a closely related and very interesting discussion on "*Unexpected deprotections of silyl and THP ethers induced by serious disparity in the quality of Pd/C catalysts*" see: Ikawa, T.; Sajiki, H.; Hirota, K. *Tetrahedron* **2004**, *60*, 6189−6195.

(16) Lipshutz, B. H.; Pallart, D.; Monforte, J.; Kotsuki, H. *Tetrahedron Lett.* **1985**, *26*, 705−708.

(17) A molecular mechanics study was performed using Allinger's MM3 force field and Still's Macromodel program: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440−467.

the lactone; the aldehyde at C11 had to be unveiled; and the last carbon, C12, had to be appended. These simple operations, summarized in Scheme 5, would complete the task of

Scheme 5



introducing the C12 methyl group and hence finalize the total synthesis. The first of these requirements was met by a standard procedure in which **15** was treated with mild base (K_2CO_3, MeOH−H_2O (10:1), 25 °C, 1.5 h); this allowed the formation of spirolactone **16** in 99% yield. A mercury-assisted hydrolysis ($HgCl_2$−$CaCO_3$, acetone−water, 10:1, reflux, 1.5 h) followed, affording the desired aldehyde **17** in 84% yield.

The final and crucial step involved the homologation at C11 for the installation of the missing carbon. This was achieved by treatment of the aldehyde **17** with Me_3Al[18] (Me_3-Al, 2.0 M, in hexanes, CH_2Cl_2, 0 °C, 20 min) to provide the corresponding methyl carbinol as an epimeric mixture (89%). Treatment of the latter with Dess−Martin periodinane in dry methylene chloride then provided **18** (87%). Removal of the silyl protecting group with HF−MeCN under the conditions specified by Coelho et al. furnished the desired alcohol, which gave characterization data that matched those reported for the synthetic but not the natural product (especially ^{13}C resonances for C1 and C2 carbons). This was shown to be the C1-βOH norsesquiterpene spirolactone **3** by measurements of spatial proximity effects (NOESY spectra) as well as by an X-ray analysis. Indeed, recrystallization of **3** from ether−heptane afforded a crystalline material suitable for X-ray diffraction analysis (Figure 2, X-ray structure of the final molecule). Our enantioselective synthesis proves that the Su group that isolated this compound incorrectly ascertained the configuration of the C1 hydroxyl group.[19]

Thus, a versatile entry to the norsesquiterpene spirolactone skeleton was achieved, starting from the Wieland−Miescher ketone, with complete control of all four contiguous stereocenters.

(18) (a) Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1979**, *44*, 4792−4797. (b) Allen, J. L.; Paquette, K. P.; Porter, N. A. *J. Am. Chem. Soc.* **1998**, *120*, 9362−9363.

(19) The optical rotation measured for the synthetic compound (+39 c = 0.043, MeOH; α_D+ 26 c = 1.01, MeOH) was not in agreement with that reported in the literature (lit. $[\alpha]_D$ −7.8 c = 0.041, MeOH) nor was the melting point (lit. 44.5−47°C; this work, 92−93°C).

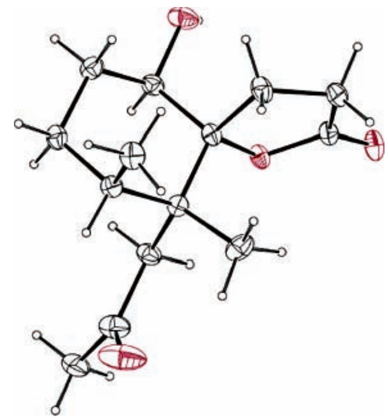


Figure 2. ORTEP view of the molecular structure of **3**.

The racemic synthesis of (±)-**1a**, and allegedly of (±)-1-*epi*-pathylactone A, by Coelho et al. has raised doubts about the spectral assignments of the natural product and showed that the structure of **1a** was erroneously established at the C1 level.

The centerpiece of this approach, which reduced to zero the number of steps involving diastereomeric separations of elaborated intermediates, was the efficient stereocleaning following the oxidative cleavage leading to a stereopure domino product **6**. The latter allows the oxygen functionality to be placed in the appropriate position and in the required relative configuration. This protocol satisfies Tietze's criteria in that it uses a nontoxic reagent as the domino promoter, generates inoffensive byproducts, produces high yields, and introduces optical purity in very early stages. The ease and versatility of this sequence rest, in large measure, in the fact that the carbon−carbon bond-forming reactions for the missing carbons are simple Wittig-type olefinations (C7, C8, and C13 additions) and an efficient C12 homologation using $AlMe_3$ as the methylating reagent.

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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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