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Total Synthesis and Elucidation of the Absolute Configuration of the Diterpene Tonantzitlolone†

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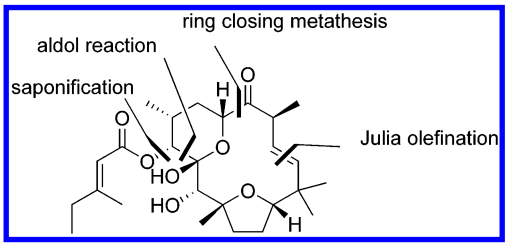
ABSTRACT



The first enantioselective total synthesis of tonantzitlolone, a novel 15-membered macrocyclic diterpene, utilized a Julia olefination, a highly selective, potassium enolate-based *anti*-Felkin aldol reaction, and an *E*-selective ring-closing metathesis as key C–C bond-forming steps. The absolute configuration of tonantzitlolone is established.

In 1990, X. A. Dominguez et al. (Departamento de Quimica, ITESM, Monterrey, Mexico) isolated a new natural compound from the endemic Mexican plant *Stillingia sanguinolenta*.[1,2] The structure (**1**, Figure 1) was elucidated in a cooperation with J. Jakupovic, and the new diterpene of unknown absolute configuration was named tonantzitlolone. In 1997 in the course of a detailed reinvestigation of the same plant, Jakupovics and Jeske[2] obtained a second derivative (OAc at C-4′ of side chain) of tonantzitlolone along with a series of other common diterpenes.[2] Tonantzitlolone contains a 15-membered carbocyclic ring that so far has only been found once before in nature in the macrocycle flexibilene **2**.[3] The highly oxygenated diterpene **1** contains strong internal hydrogen bonds between the hydroxy group at C-10 and the ester oxygens of the side chain and in particular between the lactol hydroxy group and the furan oxygen atom.[2] This network of hydrogen bonds gives the

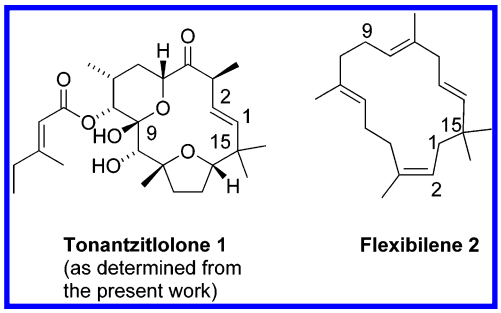


Figure 1.

† Dedicated to Prof. Dr. H. G. Floss on the occasion of his 70th birthday.
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(1) Roots of these plants were used by native Mexicans, Navajos, and Creeks in poultices of children, and the leaves were employed to treat pulmonany ailments.

(2) Jeske, F. Ph.D. Thesis, Technische Universität Berlin, Berlin, Germany, 1997.

(3) Herin, M.; Colin, M.; Tursch, B. *Bull. Soc. Chim. Belg.* **1976**, *85*, 707−719. Kazlauskas, R.; Murphy, P. T.; Wells, R. J.; Schönholzer, P.; Coll, J. C. *Aust. J. Chem.* **1978**, *31*, 1817−1824.

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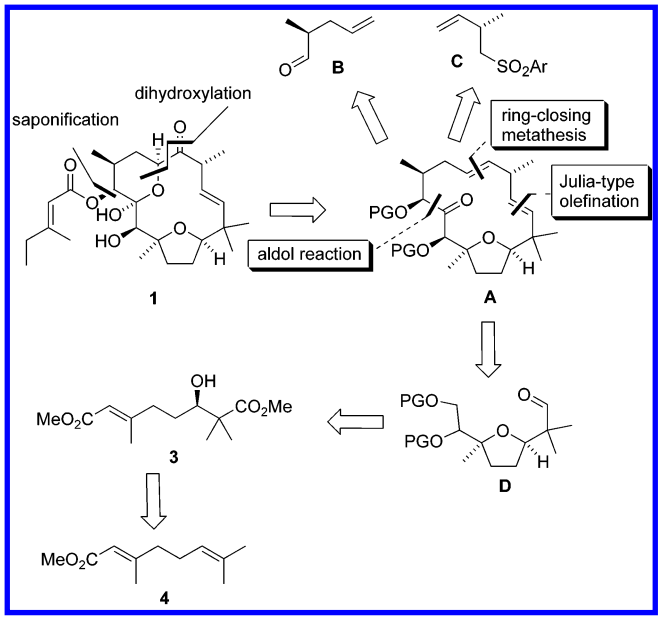
macrocyle a very rigid, almost globular overall structure. This compactness is further enhanced by a set of five methyl substituents that branch off the macrocycle. First biological tests revealed moderate cytotoxic activity of $IC_{50} = 43\ \mu M$ on PtK_2 potoroo cells.[4]

Recently, we described the synthesis of the complete carbon backbone of **1** as an acyclic precursor.[5] It was planned to cyclize this precursor by ring-closing metathesis (RCM),[6] thus forming the double bond at C-1 and C-2. Unfortunately, efforts to force macrocyclization by RCM or McMurry reaction were unsuccessful probably due to steric congestion created by the three allylic methyl groups. Therefore, we altered our synthetic strategy by shifting the position of macrocyclization to the less congested site at C-4 and C-5 (Scheme 1). In our retrosynthetic analysis, we first planned

Scheme 1. Retrosynthetic Analysis (Total Synthesis Was Conducted toward **1** with the Configuration Depicted in This Scheme)[a]

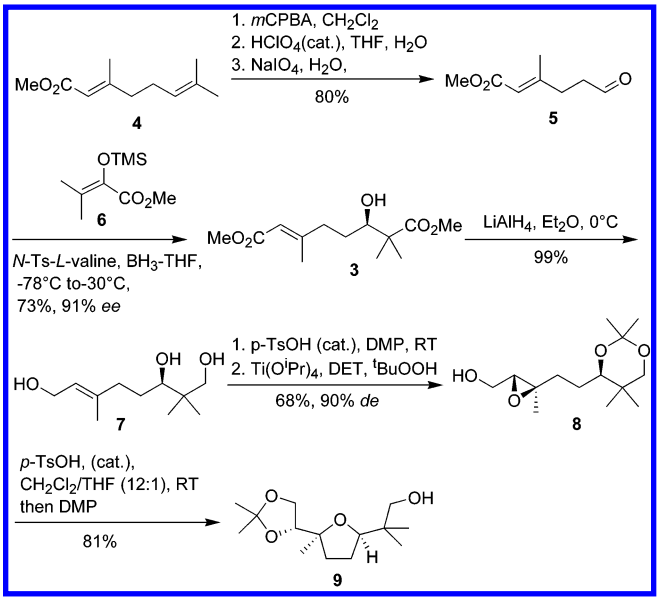


[a] PG = protective group. Ar = aryl.

to cleave the (*E*)-3-methyl-pent-2-enoic acid side chain along with removal of the oxygen functionalities at C-4 and C-5 to create macrocycle **A** as a key precursor. The macrocyclization was planned to be achieved by ring-closing metathesis, so an acyclic precursor was required that could be further dissected into three fragments **B**,[7] **C**, and **D**. While the former two fragments could readily be prepared, the southern hemisphere **D** was further simplified to the methyl ester **3** and hence to methyl geranate **4**, which served as starting material.

As the absolute configuration of tonantzitlolone **1** was unknown and no precedence of a structurally related diterperne was known, we had to arbitrarily choose one target enantiomer as depicted in Scheme 1. Thus, aldehyde **5** was prepared from methyl geranate **4** as described in the literature[8] and was subjected to the Kiyooka aldol protocol[9] using ketene acetal **6**, which yielded the diester **3** in good yield and stereoselectivity (91% ee; determined by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$ (Scheme 2).

Scheme 2[a]



[a] *m*CPBA = *meta*-chloroperbenzoic acid. Ts = *p*-toluene sulfonyl. DMP = 2,2-dimethoxy propane. DET = (−)-diethyl-D-tartrate.

Exhaustive reduction to the triol **7**, followed by protection of the 1,3-diol to the corresponding 1,3-dioxolane, set the stage for introducing the oxirane ring using the Sharpless−Katsuki protocol.[10] The resulting epoxy alcohol **8** was cyclized and reprotected in one pot by treatment with dimethoxy propane under acidic conditions. The sequence consisted of activation of the epoxide and intramolecular attack by a 5-*exo*-*tet* cyclization of the 1,3-dioxolane ring onto the preferred carbenium ion, which created a new 1,2-diol, while the acetone was released from the other terminus of the molecule.

One driving force for this thermodynamically controlled sequence can be seen in the protection of the newly created

(4) Tests were carried out at the Gesellschaft für Biotechnologische Forschung (GBF), Braunschweig, by F. Sasse. The activity can be enhanced greatly when more water-soluble derivatives are prepared.

(5) Wittenberg, R.; Monenschein, H.; Dräger, G.; Beier, C.; Jas, G.; Jasper. C.; Kirschning, A. *Tetrahedron Lett.* **2004**, *45*, 4457−4460.

(6) (a) Prunet, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 2826−2830. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043.

(7) (a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem Soc.* **1982**, *104*, 1737−1739. (b) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem Soc.* **1988**, *110*, 2506−2526.

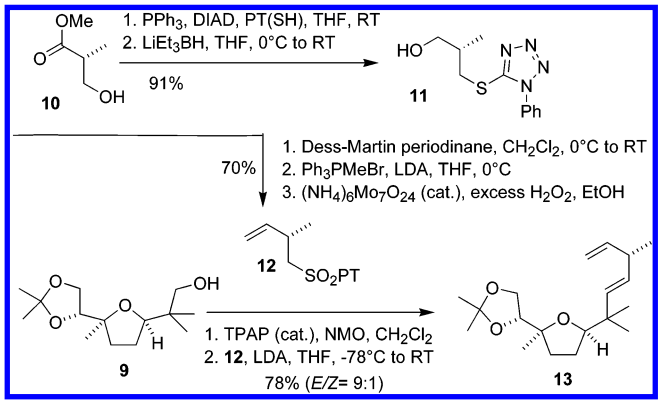
(8) Henrick, C. A.; Schaub, F.; Siddall, J. B. *J. Am. Chem. Soc.* **1972**, *94*, 5374−5378.

(9) Kiyooka, S.-i.; Hena, M. A. *J. Org. Chem.* **1999**, *64*, 5511−5523, and references therein. Machajewski, T. D.; Wong, C. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1352−1375 and references therein.

(10) (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780. (b) Marty, M.; Stoeckli-Evans, H.; Neier, R. *Tetrahedron* **1996**, *52*, 4645−4658.

1,2-diol as isopropylidene acetal. In fact, in the absence of 2,2-DMP a complex mixture of products was formed. TPAP-promoted oxidation then led to the desired aldehyde (Scheme 3).[12]

Scheme 3[a]

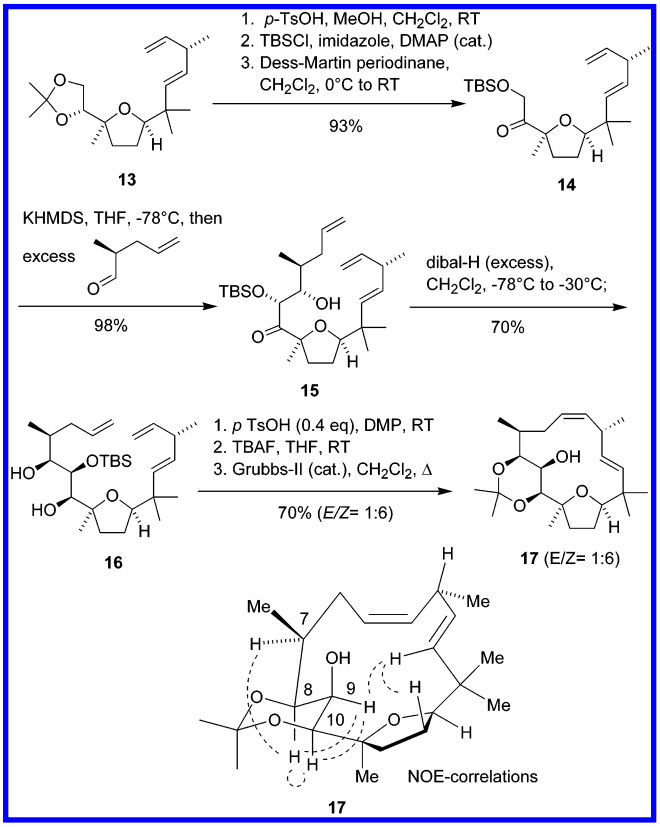


[a] DIAD = diisopropylazodicarboxylate. PT(SH) = phenyltetrazole (thiol). TPAP = tetra-*n*-propylammonium perruthenate. NMO = *N*-methylmorpholine-*N*-oxide. LDA = lithiumdiisopropylamide.

The termini of fragment **9** were sequentially elongated with building blocks **B** and **C**, the latter being added prior to aldehyde **B** by means of the Julia−Kocienski olefination.[11] Sulfone **12** was prepared from (*R*)-methyl hydroxyisobutyrate **10**, which was transformed into the phenyltetrazol thioether under Mitsunobu conditions[13] followed by reduction to yield alcohol **11** (Scheme 3). Oxidation of the alcohol, subsequent Wittig olefination, and finally oxidation of the thioether yielded sulfone **12**. This was coupled with the aldehyde derived from alcohol **9** under slightly modified conditions to the ones described before[14] (lithiumdiisopropylamide in tetrahydrofuran and warming to room temperature), which furnished the desired (*E*)-olefin **13** in excellent 92% yield (dr = 9:1).

After three functional group manipulations (deprotection, silylation, and oxidation), ketone **14** was obtained, which set the stage for the key aldol reaction with aldehyde **B** (Scheme 4).[15] KHMDS proved to be the best choice for the deprotonation of ketone **14** and the following aldol reaction with aldehyde **B**. Remarkably, the adduct **15** was isolated as a single diastereomer in excellent 98% yield.[16] The stereochemical outcome of the reaction could only be

Scheme 4[a]



[a] TBSCl = *tert*-butyl-dimethylsilyl chloride. KHMDS = potassium hexamethyldisilazide.

elucidated after 1,3-syn-reduction to the corresponding diol,[17] which then was protected as cyclic acetal **16**. After desilylation, ring-closing olefin metathesis using the 2nd generation Grubbs catalyst preferentially yielded the macrocyclic *Z*-configured diene **17**. The rigidity of the macrocycle as well as the dioxolane ring allowed proof of the desired relative 7,8-anti-8,9-syn stereochemical relationship created during the aldol reaction to **15** by means of observed NOE correlations and H−H coupling constants and by analyzing the ^{13}C shifts with the Evans−Rychnovsky method.[18,19]

The synthesis was finalized starting from diol **16**, which had been obtained after 1,3-syn reduction of **15** (see Scheme 4). In fact, we had to return to this point of the synthesis, as it is known that cis-disubstituted olefins such as **17** are difficult to asymmetrically dihydroxylate.[20] And indeed, macrocycle **17** could not be oxidized, neither with OsO_4 nor under the Sharpless conditions.

(11) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563−2585 and references therein.

(12) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666.

(13) (a) Mitsunobu, O. *Synthesis* **1981**, 1−28. (b) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487−6491.

(14) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26−28.

(15) (a) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191−1223. (b) Marco, J. A.; Carda, M.; Díaz-Oltra, S.; Murga, J.; Falomir, E.; Roeper, H. *J. Org. Chem.* **2003**, *68*, 8577−8582. (c) Evans, D. A.; Siska, S. J.; Cee, V. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 1761−1765.

(16) Detailed mechanistic discussion on this aldol reaction will be presented in a full account.

(17) Reaction did not always proceed to completion. In these cases, recovered starting material can be resubjected to enhance material throughput.

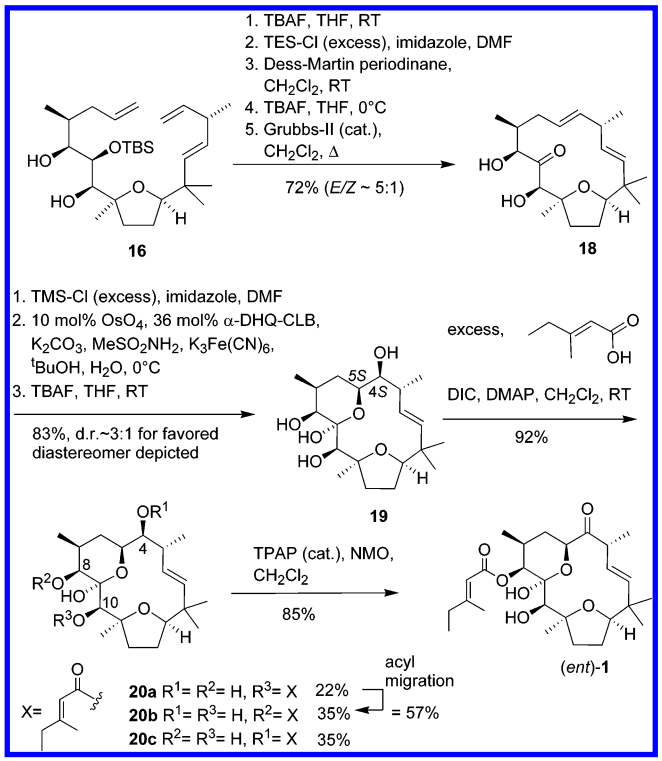
(18) Observed coupling constants along the C-7−C-10 chain: δ = 1.91−2.06 (m, 2 H; H-7, 9-OH), 3.28 (br s, 1 H, H-10), 3.69 (d, $J_{7,8}$ = 6.1 Hz, 1 H; 8-H), 3.92 (d, $J_{9,OH}$ = 11.3 Hz, 1 H, H-9); no H−H coupling constants between C-8/C-9 and C-9/C-10 are observed, which supports the suggested conformation depicted in Scheme 4.

(19) Determination of the 8,10-syn-relationship: (a) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099−7100. (b) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511−3515.

(20) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

Removal of the TBS group in **16** yielded the corresponding triol, which could be selectively silylated at the terminal hydroxy groups, followed by oxidation at the central position with the Dess−Martin periodinane. Deprotection to the corresponding dihydroxy ketone and ring-closing metathesis then furnished macrocycle **18**, now with high *E*-selectivity (Scheme 5).

Scheme 5[a]



[a] DHQ-CLB = *O*-(4-chlorobenzoyl)hydroquinine. DIC = diisopropylcarbodiimide. DMAP = (dimethylamino)pyridine.

Studies to selectively introduce the side chain prior to oxidation of the newly formed double bond proved to be ineffective. We therefore dihydroxylated the C-4/C-5 double bond first without affecting the sterically encumbered double bond at C-1/C-2. The best stereoselection (dr for 4*S*,5*S*/4*R*,5*R* = 3:1) was achieved when the two hydroxy groups in **18** were first protected as TMS ethers. The resulting diol had to be completely desilylated prior to lactol formation, which yielded triol **19**. With this macrocycle at hand, all stereogenic centers of the natural product were set up. In the following, no protecting group strategy tested allowed the efficient differentiation of the three hydroxy groups. We therefore decided to directly esterify triol **19**, which furnished all three possible regioisomers in an overall yield of 92%.[21] Due to the 1,3-syn relationship of the oxygen functionalities in **20a**, the ester side chain at C-10 tended to migrate to the C-8 position. This migration could be effected quantitatively by addition of a catalytic amount of DMAP to a solution of **20a**, thereby improving the yield to 57% in favor of **20b**. The final oxidation to the natural product was selectively carried out with TPAP, providing the (*ent*)-tonantzitlolone **1** as was judged from the optical rotation (authentic natural product, $[\alpha]^{20}_D = +134°$ (*c* 0.25, $CHCl_3$); found, $[\alpha]^{20}_D = -119°$ (*c* 0.06, $CHCl_3$)). Apart from these facts, all spectroscopic data (NMR, IR, MS) were in full accordance with those of the authentic material.[2]

In conclusion, we achieved the first total synthesis of the novel diterpene tonantzitlolone **1** and, importantly, elucidated its absolute configuration. The synthesis is highly selective and relies on the effective use of substrate-controlled reactions that allow the introduction of the stereogenic centers in the northern and the western region of **1**. Details on the biological properties and the biological target of tonantzitlolone, its (−)-enantiomer, and various derivatives will be reported in a full account.

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Supporting Information Available: Descriptions of experimental procedures as well as analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Regioisomeric esters were separable after the oxidation that followed.