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Determination of the absolute configuration of the diterpene tonantzitlolone B

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ABSTRACT

In this work synthetic and semi-synthetic studies toward the antitumor active natural product tonantzitlolone B are described, starting with an advanced intermediate obtained from the total synthesis of tonantzitlolone and a natural sample of this compound, respectively. The unknown absolute configuration of the stereogenic center in the side chain was elucidated to be (*R*).

Tonantzitlolone (**1**) and Tonantzitlolone B (**2**) (Fig. 1) were isolated from the Mexican plant *Stillingia sanguinolentia*.[1] The roots and leaves of *S. sanguinolentia* have been used for the treatment of various medical purposes by the Mexican natives, and similar applications of *S. sylvatica* by Navajo and Creek Native Americans have been reported. Primary biological tests showed activity and selectivity of **1** and **2** against human kidney and breast cancer cell lines.

The total synthesis of (*ent*)-Tonantzitlolone (*ent*-**1**) was recently accomplished in our laboratories and established the depicted absolute configuration of the macrocycle.[2]

Since the absolute configuration of the side chain of Tonantzitlolone B (**2**) was still unknown and could not be determined spectroscopically, a synthetic approach toward **2** was pursued. Thus, we prepared the macrocycle **3** of naturally occurring Tonantzitlolone (**1**) according to the protocol described before for *ent*-**1** (Scheme 1).[2,3] Building blocks **4**–**7** served to assemble dihydroxyketone **8** which was subjected to ring closing metathesis conditions.[4,5] The resulting macocycle **9** was further elaborated to tetraol **3** by a set of standard transformations.

At this point, the side chain of Tonantzitlolone B which had to be introduced was prepared (Scheme 2). The synthesis of both enantiomers **12a**,**b** started from methyl lactates **10a**,**b**. TBS-protection and subsequent methyl lithium addition at very low temperature delivered the protected (*R*)-configured 3-hydroxy-2-butanone which was transformed into the corresponding α,β-unsaturated ester **11a** by a Horner-Wadsworth-Emmons

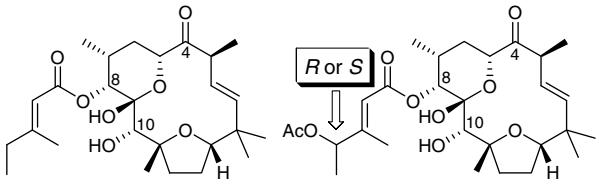

Figure 1. Tonantzitlolone (**1**) and tonantzitlolone B (**2**).

olefination. The (4*S*)-enantiomer **11b** was prepared by a modified route via the Weinreb amide (amide formation, Grignard addition, protection, HWE). However, this synthesis turned out to be longer and gave lower yields. In the following steps, TBAF-mediated desilylation, saponification, and acetylation of the hydroxy group delivered the (*R*)- and (*S*)-configured acids **12a**,**b**, respectively.

Separate coupling of **12a** and **12b** with the macrocycle **3** was achieved under conditions previously established for the synthesis of Tonantzitlolone **1**. However, a large excess of the carboxylic acid **12** and disopropylcarbodiimide (DIC) in the presence of 4-DMAP afforded a complex mixture of coupling products for both carboxylic acids **12a**,**b** (Scheme 3). After oxidation, the resulting products could not be separated by HPLC. Samples containing enriched isomers were analyzed, and from the ^{1}H NMR and the ^{1}H,^{1}H-COSY spectra it could unequivocally be concluded that all major products resulted from esterification at C-4.[6] Additionally, a remarkable correlation between the ^{1}H NMR spectrum of authentic Tonantzitlolone B (**2**) and a minor product in the ^{1}H NMR spectrum of one

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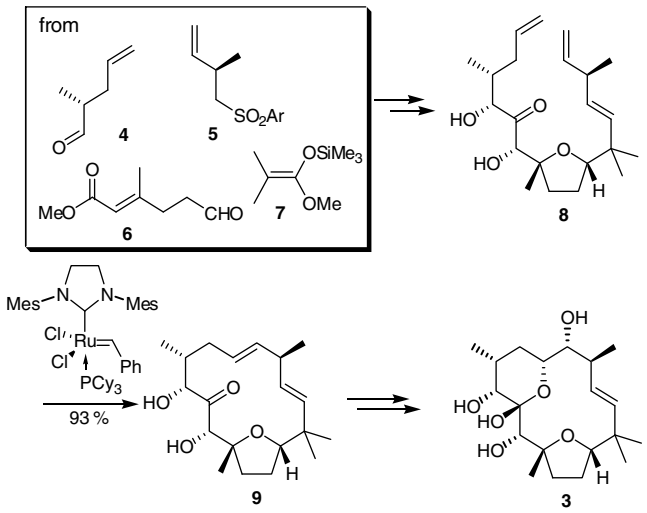
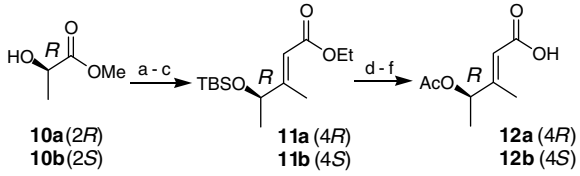
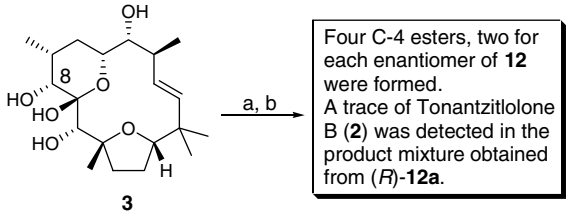


Scheme 1. Synthesis of macrocycle **3** according to Ref. 2.



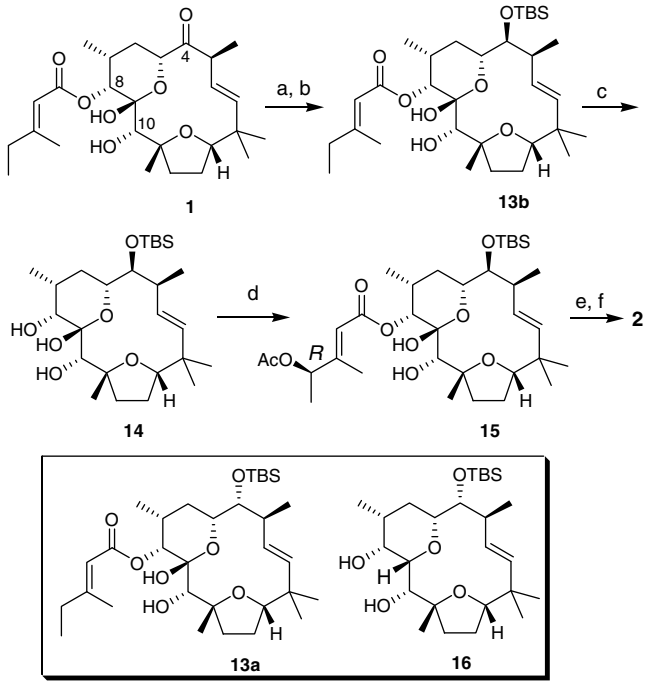
Scheme 2. Preparation of side chain **12** [only (*R*)-series shown]. Reagents and conditions: (a) DMF, imidazole, TBSCl, rt, 19 h; (b) THF, MeLi, −105 °C, 45 min, then TMSCl, −105 °C, 20 min, then HCl, rt, 1 h, >99% (2 steps); (c) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, rt, 22 h, 48%; (d) TBAF $3H_2O$, THF, rt; (e) LiOH, MeOH/H_2O 1:2, rt, 3 h; (f) Ac_2O, NEt_3, 4-DMAP, rt, 1.5 h, 36% (3 steps).



Scheme 3. Attempts of C8-esterification of **3**. Reagents and conditions: (a) 15 equiv **12a**,**b**, 15 equiv DIC, DMAP, CH_2Cl_2, rt, 4–5 h; (b) TPAP, NMO, CH_2Cl_2, rt, 0.5–1 h; for **12a**: 44% (1:1 ratio of both esters formed); for **12b**: 57% (1.2:1).

fraction [formed after esterification with (*R*)- configured **12a**] was encountered. At this point we were unable to purify and fully characterize the expected (*R*)-isomer.

In order to finally prove the (4*R*)-configuration in the side chain, we turned our attention to a semi-synthetic strategy using authentic Tonantzitlolone (**1**) as the starting point. While simple removal of the methyl senecioate side chain by transesterification or saponification turned out to be impossible, treatment with 7 equiv DIBAL led to reduction of the keto group at C-4 and to some extent to simultaneous cleavage of the ester. However, when only 1 equiv DIBAL was employed the selective reduction of the C-4 carbonyl group could be achieved to yield the epimeric alcohols which were separated by chromatography. Silylation of each alcohol yielded Tonantzitlolone derivatives **13a**,**b** (Scheme 4). Reductive removal of the methyl senecioate side chain in **13b** with 5 equiv DIBAL delivered small amounts of the mono-protected compound **14**. When epimeric **13a** was subjected to these conditions, only traces



Scheme 4. Semisynthesis of Tonantzitlolone B (**2**) from **1**. Reagents and conditions: (a) 1 equiv DIBAL, CH_2Cl_2, −78 °C to 0 °C, 30 min, 27% for α-diastereoisomer, 55% for β-diastereoisomer; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 45 min, 66% for **13a** and 71% for **13b**; (c) 5 equiv DIBAL, CH_2Cl_2, −78 °C to 0 °C, 5 h, 22%; (d) 15 equiv **12a**, 15 equiv DIC, DMAP, THF, 40 °C, 5 d; (e) TBAF·$3H_2O$, THF, rt, 17 h; (f) TPAP, NMO, CH_2Cl_2, 4 Å MS, rt, 45 min, 25% (3 steps).

of the isomeric analogue of **14** were detected. Isolation of **16** clearly revealed the principal problem of chemoselectivity associated with this step which explains the low isolated yield for **14**.

Esterification with the (*R*)-configured acid **12a** was only achieved when a large excess of acylating reagents was added portionwise over 6 h. Otherwise, we encountered substantial acylation of one diimide nitrogen atom of the DIC reagent. In the following the acylation product **15** was desilylated and selectively oxidized at C-4. The ^1H and ^{13}C NMR spectroscopic data as well as CD spectra of the resulting Tonantzitlolone derivative were compared with those of authentic Tonantzitlolone B (**2**),[7] and confirmed the depicted configuration as being the natural one (see supporting data).

In summary, we determined the absolute configuration of the ester side chain of Tonantzitlolone B utilizing two alternative synthetic strategies.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.06.105.

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6. The observation that several C-4 esters are formed upon esterification/oxidation can be explained by α-epimerization at C-8 or C-10, respectively, of the ring opened acetal or by a non-selective oxidation with respect to the position (see also Ref. 2).
7. Selected analytical data of synthetic Tonantzitlolone B (**2**): ^{1}H NMR ($CDCl_3$, 500 MHz, $CHCl_3$ = 7.26 ppm): δ_H = 5.93 (br q, *J* = 1.4 Hz, 1H, 2′-H), 5.88 (d, *J* = 15.0 Hz, 1H, 1-H), 5.73 (s, 1H, 9-OH), 5.27 (br q, *J* = 6.6 Hz, 1H, 4′-H), 5.27 (dd, *J* = 15.0, 9.7 Hz, 1H, 2-H), 4.93 (d, *J* = 2.6 Hz, 1H, 8-H), 4.66 (dd, *J* = 11.8, 2.9 Hz, 1H, 5-H), 3.80 (dd, *J* = 11.3, 5.1 Hz, 1H, 14-H), 3.43 (d, *J* = 6.4 Hz, 1H, 10-H), 3.36 (dq, *J* = 9.7, 7.0 Hz, 1H, 3-H), 3.09 (d, *J* = 6.6 Hz, 1H, 10-OH), 2.46 (br dd, *J* = 12.5, 7.5 Hz, 1H, 12-H), 2.37–2.29 (m, 1H, 7-H), 2.16 (d, *J* = 1.4 Hz, 3H, 6′-H), 2.12 (s, 3H, $COCH_3$), 2.06–1.98 (m, 1H, 13-H), 1.88–1.82 (m, 1H, 6-H), 1.80 (ddd, *J* = 5.1, 6.8, 11.5 Hz, 1H, 13-H), 1.58–1.47 (m, 1H, 12-H), 1.40 (s, 3H, 18-H), 1.40–1.32 (m, 1H, 6-H), 1.38 (d, *J* = 6.6 Hz, 3H, 5′-H), 1.17 (s, 3H, 17-H), 1.16 (d, *J* = 7.0 Hz, 3H, 20-H), 0.91 (s, 3H, 16-H), 0.87 (d, *J* = 7.0 Hz, 3H 19-H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz, $CDCl_3$ = 77.16 ppm): δ_C = 166.4 (q, 1′-C), 157.8 (q, 3′-C), 140.2 (t, 1-C), 126.9 (t, 2-C), 115.2 (t, 2′-C), 89.0 (t, 14-C), 87.6 (q, 11-C), 78.3 (t, 10-C), 74.2 (t, 5-C), 74.0 (t, 4′-C), 73.8 (t, 8-C), 49.7 (t, 3-C), 38.9 (q, 15-C), 37.5 (s, 12-C), 29.2 (t, 7-C), 28.9 (s, 6-C), 28.3 (p, 18-C), 25.6 (p, 16-C), 25.2 (p, 17-C), 19.3 (p, 5′-C), 17.2 (p, 19-C), 16.2, 15.4 (2 × p, 20-C, 6′-C) ppm. Due to the small amount of synthetic material available the following carbon atoms could not be detected in the ^{13}C NMR spectrum: 211.4, 170.1, 97.2, 28.2 and 21.4 ppm.
NMR data of authentic Tonantzitlolone B (**2**).^{1}H NMR ($CDCl_3$, 500 MHz, $CDCl_3$ = 7.26 ppm): δ_H = 5.93 (br q, *J* = 1.3 Hz, 1H, 2′-H), 5.88 (d, *J* = 15.3 Hz, 1H, 1-H), 5.71 (s, 1 H, 9-OH), 5.27 (br q, *J* = 6.6 Hz, 1H, 4′-H), 5.24 (dd, *J* = 15.2, 9.6 Hz, 1H, 2-H), 4.93 (d, *J* = 2.8 Hz, 1H, 8-H), 4.66 (dd, *J* = 11.9, 2.8 Hz, 1H, 5-H), 3.80 (dd, *J* = 11.3, 5.2 Hz, 1H, 14-H), 3.43 (d, *J* = 6.6 Hz, 1H, 10-H), 3.33 (dq, *J* = 9.5, 6.8 Hz, 1H, 3-H), 3.06 (d, *J* = 6.6 Hz, 1H, 10-OH), 2.43 (br dd, *J* = 12.5, 7.4 Hz, 1H, 12-H), 2.37–2.29 (m, 1H, 7-H), 2.13 (d, *J* = 1.4 Hz, 3H, 6′-H), 2.10 (s, 3H, $COCH_3$), 2.06–1.97 (m, 1H, 13-H), 1.87–1.82 (m, 1H, 6-H), 1.77 (ddd, *J* = 5.3, 7.0, 12.0 Hz, 1H, 13-H), 1.57–1.48 (m, 1H, 12-H), 1.37 (s, 3H, 18-H), 1.40–1.33 (m, 1H, 6-H), 1.35 (d, *J* = 6.6 Hz, 3H, 5′-H), 1.14 (s, 3H, 17-H), 1.13 (d, *J* = 7.0 Hz, 3H, 20-H), 0.91 (s, 3H, 16-H), 0.85 (d, *J* = 7.0 Hz, 3H 19-H) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz, $CDCl_3$ = 77.16 ppm): δ_C = 211.4 (q, 4-C), 170.1 (q, $COCH_3$), 166.4 (q, 1′-C), 157.8 (q, 3′-C), 140.2 (t, 1-C), 126.9 (t, 2-C), 115.2 (t, 2′-C), 97.2 (q, 9-C), 89.0 (t, 14-C), 87.6 (q, 11-C), 78.3 (t, 10-C), 74.2 (t, 5-C), 73.9 (t, 4′-C), 73.8 (t, 8-C), 49.7 (t, 3-C), 38.9 (q, 15-C), 37.4 (s, 12-C), 29.2 (t, 7-C), 28.9 (s, 6-C), 28.3 (p, 18-C), 28.2 (s, 13-C), 25.6 (p, 16-C), 25.2 (p, 17-C), 21.4 (p, $COCH_3$), 19.3 (p, 5′-C), 17.2 (p, 19-C), 16.2, 15.4 (2 × p, 20-C, 6′-C) ppm.
HRMS-ESI ($C_{28}H_{42}O_9$): calcd 545.2727 $[M+Na]^+$, found 545.2726.