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Tandem Intermolecular Alkylation-Intramolecular Robinson Annelation: A Novel and Stereoselective Construction of the Octalin Skeleton —Expeditious Synthesis of (–)-Tanabalin —

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Abstract: Tanabalin (**1**), an insect antifeedant, was synthesized in optically active form employing a known δ-lactone (**F**) as the only source of chirality. The key step is a tandem intermolecular alkylation-intramolecular Robinson annelation to construct the *trans*-octalin skeleton.

In 1996, Kubo, Kusumi *et al.* isolated and fully characterised a novel clerodane diterpenoid, tanabalin (**1**), from the dried flower of a Brazilian medicinal plant, *Tanacetum balsamita*.[1]. Tanabalin (**1**) exhibits potent insect antifeedant activity against pink bollworm, *Pectinophora gossypiella*, a severe cotton pest. This remarkable bioactivity of **1** made this an attractive synthetic target. Herein, we wish to report an efficient construction of the *trans*-octalin skeleton (**B**) and its subsequent transformation into the natural enantiomer of **1**.

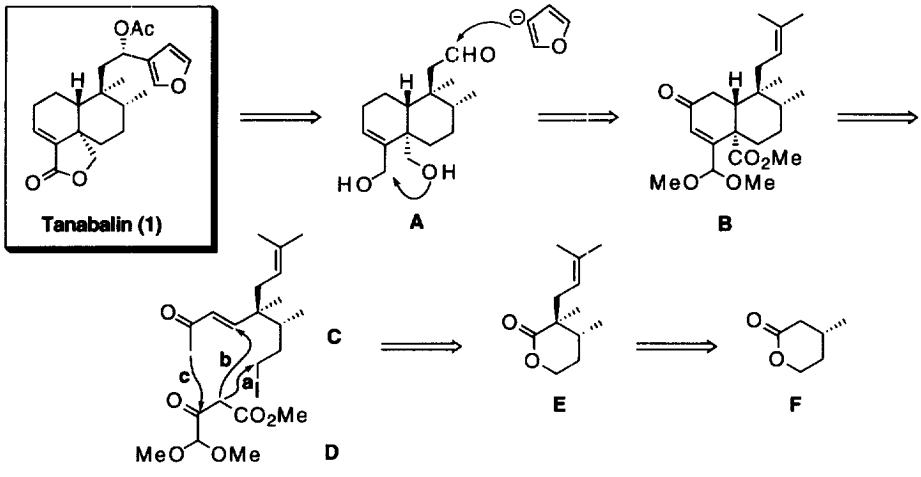

Fig. 1.

Our synthetic strategy is shown in Fig. 1. It was clear that a late stage addition of a furyl anion to an aldehyde such as **A** with a suitably substituted *trans*-octalin ring system and an oxidative lactone formation should give tanabalin (**1**). The key step in our sequence was the novel construction of the *trans*-octalin skeleton of **B**. We envisaged that a tandem reaction sequence could indeed construct the desired skeleton in a single

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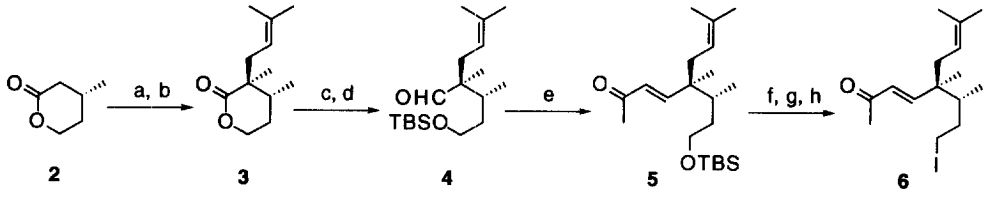
operation. We believed that treatment of the known β-keto ester (**D**)[2] with iodide (**C**) under basic conditions would facilitate a sequential intermolecular alkylation (**a**) followed by intramolecular Robinson annelation [Michael addition (**b**) and aldol reaction (**c**)] to give the desired skeleton in one pot. Two new stereogenic centers at the angular position of the *trans*-octalin skeleton (**B**) are introduced in this sequence and we assumed that the product (**B**) would predominate under the thermodynamically controlled Michael addition (**b**). The iodide (**C**) was clearly derivable from lactone (**E**) *via* reductive ring opening followed by Wittig-type olefination. Thus, the known (*R*)-3-methyl-5-pentanolide (**F**)[3] was selected as the starting material for our route. Described below is the complete scheme of the synthesis of tanabalin.



a) LDA, MeI, THF-HMPA, 86%; b) LDA, prenyl bromide, THF-HMPA, 92%; c) DIBAL, toluene, 97%; d) TBSCl, Imid., DMF, quant.; e) $(MeO)_2P(O)CH_2COCH_3$, *n*-BuLi, toluene, reflux, 97%; f) HF-Et_3N, MeCN, 90%; g) CBr_4, Ph_3P, Et_3N, CH_2Cl_2, 82%; h) NaI, Me_2CO, quant.

Fig. 2.

The first stage of our synthesis was the preparation of the precursor [**6** (=**C**)] for cyclization (Fig. 2). Sequential highly diastereoselective enolate alkylations of **2**[3f] with MeI and prenyl bromide using LDA and HMPA (1.0 eq.) in THF afforded **3** as the sole stereoisomer in 79% overall yield. After reduction of **3** with diisobutylaluminum hydride (DIBAL) at -78℃, the resulting lactol was treated with *t*-butyldimethylsilyl (TBS) chloride in DMF to afford aldehyde (**4**) in 97% combined yield. The Horner-Wittig reaction of **4** gave enone (**5**) in 97% yield, which was subsequently converted to the corresponding iodide (**6**) in three steps in 74% yield. Bromination had to be done immediately after the liberation of hydroxyl group by fluoride treatment to avoid tetrahydropyran formation *via* the Michael type addition of the free hydroxyl group.

The second stage of our synthesis was the conversion of **6** to *trans*-octalin [**8** (=**B**)] as shown in Fig. 3. This tandem reaction was a critical step and the best result was obtained when a mixture of iodide [**6** (=**C**)] and β-keto ester [**7** (=**D**), 10eq.] was heated at 50℃ with sodium methoxide (10eq.) in methanol. The desired *trans*-octalin was obtained as a single stereoisomer in 82% yield. In this reaction sequence, the second step, the reversible intramolecular Michael addition (**9**→**10**), determines the stereochemistry of the product. The extreme high stereoselectivity in this step can be explained not only thermodynamically but also kinetically as depicted in Fig. 3. In the transition state (**G**), the bulky prenyl group fixes the molecule as shown and maximum overlap between the HOMO of the enolate and the LUMO of the enone results in the formation of the most stable "pseudo" *trans*-octalin intermediate, in which the methyl group at C-6 and the prenyl group at C-7 are located in equatorial position. The relative stereochemistry of **8** was confirmed by ^{1}H-NMR NOE experiments.

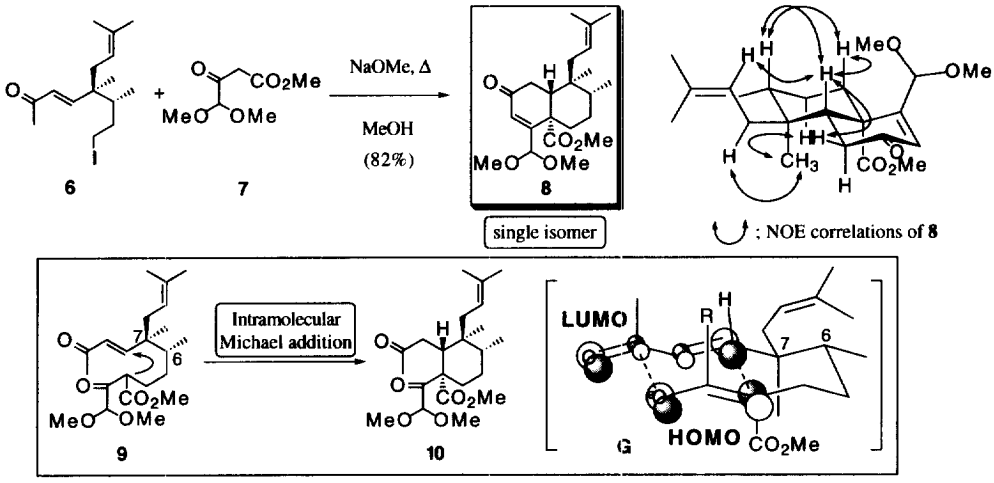
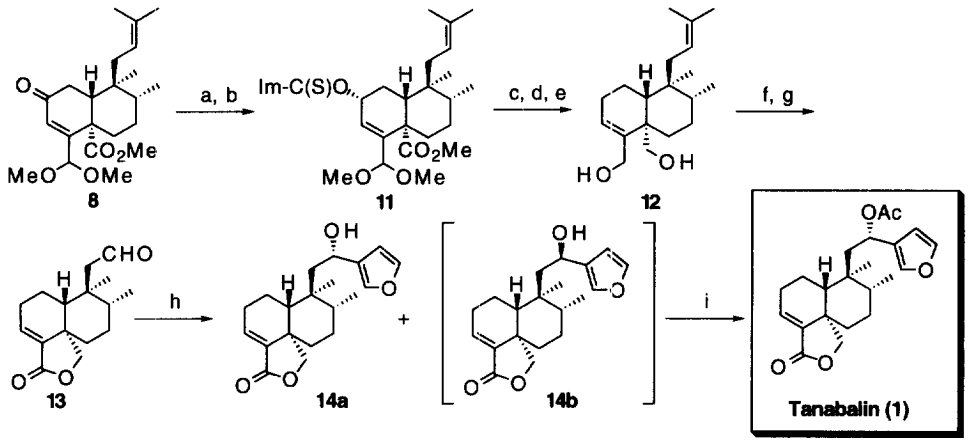


Fig. 3.

The final stage of our synthesis was the conversion of **8** to tanabalin (**1**) as shown in Fig. 4. The carbonyl group of **8** was firstly reduced using DIBAL and then deoxygenated using Barton's procedure[4] *via* the corresponding thiocarbamate (**11**). Subsequent acetal hydrolysis followed by DIBAL reduction gave diol (**12**) in 45% yield for 5 steps. Oxidation of **12** with the Fetizon reagent (Ag_2CO_3 on Celite®)[5] gave a γ-lactone directly, which provided aldehyde (**13**) by careful ozonolysis in 82% yield. Reaction with 3-furyllithium[6] gave a 1:1 mixture of epimeric alcohols (**14a**[7] and **14b**) in 68% yield. Although stereoselectivity was absent in this step, these stereoisomers were separable by SiO_2 column chromatography. Finally, acetylation of **14a** afforded the target compound, tanabalin (**1**) in quantitative yield; $[\alpha]_D^{20}$ -112 (*c* 0.28, $CHCl_3$) [lit.[1]: $[\alpha]_D$ -132 (*c* 0.1, $CHCl_3$)]. The ^{1}H-NMR spectrum of the synthetic **1** was identical with that of the natural tanabalin[1].



a) DIBAL, toluene, 88%; b) Im-C(S)-Im, benzene, 68%; c) *n*-Bu_3SnH, AIBN, benzene; d) AcOH, H_2O, MeOH, 93% (2 steps); e) DIBAL, toluene, 83%; f) Ag_2CO_3-Celite®, benzene, 89%; g) 1 eq. O_3, $NaHCO_3$, MeOH; Me_2S, 82%; h) 3-furyllithium, THF, 34% of **14a** and 34% of **14b**; i) Ac_2O, Pyr., quant.

Fig. 4.

In conclusion, the first total synthesis of natural (–)-tanabalin was accomplished effectively by using a novel stereoselective tandem intermolecular alkylation-intramolecular Robinson annelation. The overall yield was 5% over 18 steps. The transformation of alcohol (**14b**) into **14a** or **1** is currently under progress.

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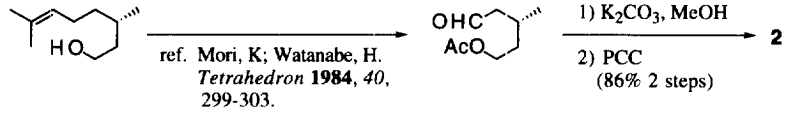
   (f) We prepared the known lactone (**2**) from (–)-citronellol of 98% e.e. as shown below:



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   Alcohol (**14a**) was isolated from *Heteropapapus altaicus*, and characterised by Huneck *et al.* The ^{1}H-NMR and IR data of the alcohol (**14a**) were identical with those of the natural **14a**.