An Enantioselective Formal Total Synthesis of (–)-TAN1251A

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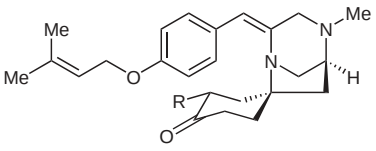
Dedicated to Professor Clayton H. Heathcock in honour of his many outstanding contributions to organic chemistry

Abstract: An enantioselective total synthesis of the muscarinic inhibitor (–)-TAN1251A has been achieved. An alkylidene 1,5-CH insertion reaction was used as a key step to produce a [5,5]-spirocyclic intermediate, which was transformed into the [6,5]-spirocyclic core of the natural product via an oxidative cleavage/aldol condensation sequence. The synthesis of the natural product was then completed using standard procedures.

Key words: total synthesis, alkaloid, carbene insertion, asymmetric synthesis, spiro compounds

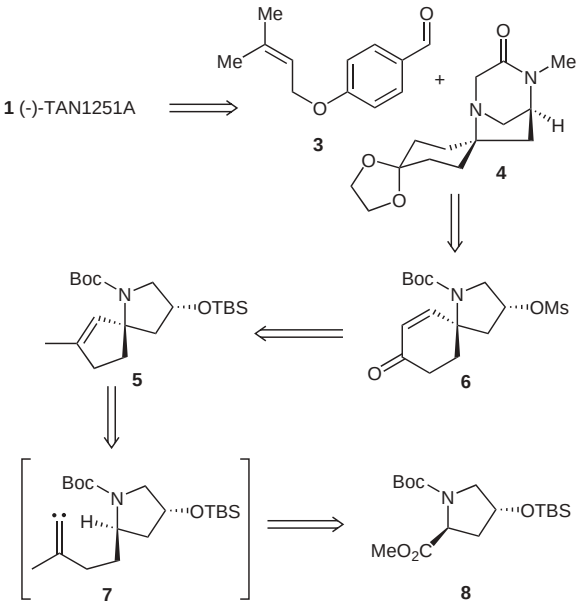
The alkaloids TAN1251A **1** and TAN1251B **2** (Figure 1) were isolated from a culture of *Penicillium thomii* RA-89 by researchers at Takeda Chemical Industries Ltd.,[1] and they possess potent cholinergic activity. TAN1251A is a selective inhibitor of the M_1 muscarinic receptor subtype and the affinity of TAN1251B to a muscarinic acetylcholine receptor is stronger than that of atropine.



1 (-)-TAN1251A R=H
2 (+)-TAN1251B R=OH

Figure 1

Since their appearance in the patent literature, **1** and **2** have attracted attention from synthetic organic chemists and five total syntheses of TAN1251A (**1**) have been published to date.[2] TAN1251B (**2**) has proved to be a more challenging synthetic target due to the presence of a nitrogen-bearing quaternary stereocentre. In fact, only Snider[2b] has reported a synthesis of **2** via the α-hydroxylation of TAN1251A (**1**), and this transformation could only be accomplished in modest yield. Several years ago we initiated a research programme examining the synthesis of target structures that contained nitrogen-bearing quaternary stereocentres as a key structural feature, and we found that alkylidene carbenes could be used to solve this synthetic problem.[3] Our studies had shown that [5,5]-spirocyclic structures were especially easy to construct using a 1,5-CH insertion reaction and that these materials could be transformed into a range of interesting amino acid target structures. Upon examining the structures of TAN1251A (**1**) and B (**2**) we realised that an alkylidene carbene insertion reaction could also be used indirectly to access the [6,5]-spirocyclic core of these natural products and our retrosynthetic analysis is outlined in Scheme 1.



Scheme 1

Following the precedent set by Kawahara et al.,[2a] we first disconnected (–)-TAN1251A (**1**) to reveal the aldehyde **3** and the [6,5]-spirocyclic fragment **4** as key late-stage intermediates. Further disconnection of **4** via cleavage of the bridged bicyclic moiety identified the cyclohexenone **6** as an important spirocyclic building block. We envisaged that **6** could be accessed from the [5,5]-spirocycle **5** via an oxidative cleavage-aldol condensation sequence.[4] The spirocycle **5** would be constructed using an alkylidene carbene 1,5-CH insertion reaction via **7**, and the cyclisation precursor should be readily available from a suitably protected *trans*-hydroxyproline derivative **8**.[5] We were particularly attracted to this synthetic route as the cyclohexenone **6** should be produced in high enantiomeric and diastereomeric excess, and will afford us the opportunity to access TAN1251B (**2**) via conversion of the enone into an α-hydroxy ketone.[6]

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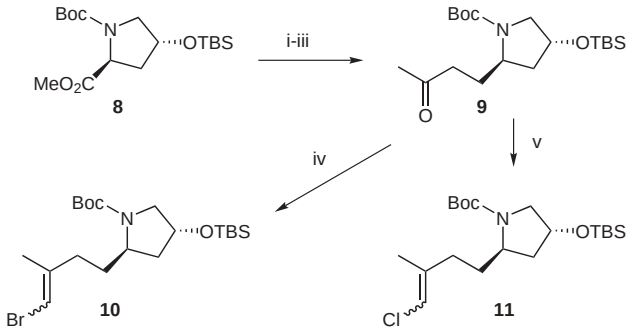
The synthesis of TAN1251A (**1**) began with the preparation of **8** from *trans*-4-hydroxyproline using standard procedures.[5] The ester **8** was then partially reduced with DIBALH to afford the corresponding aldehyde, which was then treated with (acetylmethylene)triphenylphosphorane to give the resulting α,β-unsaturated ketone in excellent yield. Catalytic hydrogenation (Pd/C, H_2, EtOAc) of the enone then provided the ketone **9** in quantitative yield. Having developed an efficient route to **9**, we were able to synthesise the vinylbromide **10** and the vinylchloride **11** via simple Wittig olefination chemistry. This sequence could be performed on large scale and multigram quantities of the three alkylidene carbene cyclisation precursors **9**, **10** and **11** could be prepared easily (Scheme 2).

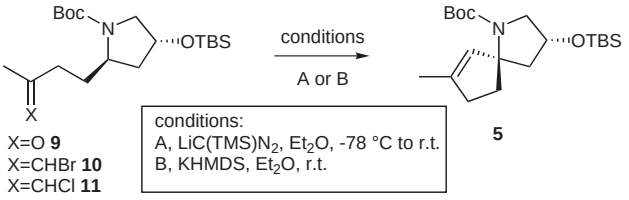


Scheme 2 *Reagents*: (i) DIBALH, CH_2Cl_2, –78 °C; (ii) $Ph_3PCHC(O)CH_3$, CH_2Cl_2 (91%, 2 steps); (iii) Pd/C, H_2, EtOAc (100%); (iv) $(Ph_3PCH_2Br)Br$, KHMDS, THF (79%), (1.3:1 *E*:*Z*); (v) $(Ph_3PCH_2Cl)I$, KHMDS, THF (100%), (2.4:1 *E*:*Z*)

We were now in a position to examine the key 1,5-CH insertion reaction and we first chose to examine the cyclisation of **9**. Following the standard procedure as described by Ohira,[7] **9** was added to a preformed solution of lithiated TMS-diazomethane at low temperature (–78 °C) and the resulting solution was allowed to warm to room temperature. Nitrogen gas was evolved during the warming process, which is indicative of the alkylidene carbene **7** being formed in solution. Once the reaction was judged complete by TLC analysis, we were pleased to find that the desired [5,5]-spirocyclic product **5** was produced as the major new product in modest to excellent yield (40–86%).

Although, we were pleased by this initial success, the large variation in isolated yield of **5** was not acceptable and we decided to examine the use of the vinyl halides **10** and **11** as cyclisation precursors. Pleasingly, both **10** and **11** proved to be good substrates for the CH-insertion reaction and treatment of either compound with KHMDS in Et_2O[8] afforded the desired spirocycle **5** as the major new product.[9] Separation of the *E*- and *Z*-olefin isomers of **10** and **11** proved to be quite difficult on large scale,[10] but we found that the *E*:*Z* ratio of the starting vinyl halide made little or no difference to the isolated yield of the cyclised products (see Table 1). Our best results were obtained using the vinylchloride **11** as the CH-insertion precursor and consistently high yields could be obtained in the cyclisation reaction. Even on large scale, we were able to obtain excellent yields for the formation of **5**. In one reaction we

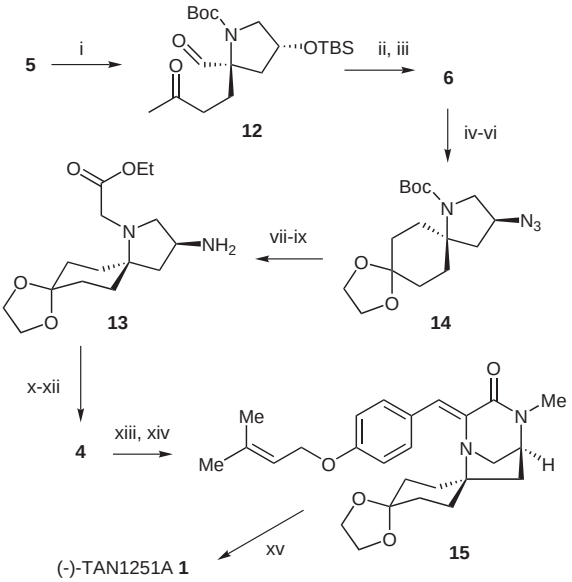
Table 1 The Key 1,5-CH Insertion Reaction



Cyclisation precursor	*E*:*Z* ratio	Conditions	Isolated yield of **5** (%)
9	N:A	A	40–86
10	1:0	B	68
10	9:1	B	73
10	1:2	B	66
11	2.4:1	B	93

were able to cyclise a single 84 g batch of **11** and we obtained a 78% yield of the [5,5]-spirocycle **5**. All of these reactions were performed at between 0 °C and room temperature, and there were no obvious scale-up problems. In all cases we obtained **5** as a single diastereoisomer, thus indicating that the CH-insertion process had proceeded with the expected high level of stereoselectivity.

Having developed an efficient route to the [5,5]-spirocycle **5** we were now ready to explore the remaining steps needed to complete a synthesis of (–)-TAN1251A (**1**). The first task was to perform a ring expansion reaction to



Scheme 3 *Reagents*: (i) $K_2OsO_4{\cdot}H_2O$, NMO, acetone–H_2O then $NaIO_4$, THF–H_2O (74%, 2 steps); (ii) KOH (5% aq), CH_2Cl_2, TBAB (67%) or TBAF (1 M in THF), THF (89%); (iii) MsCl, Et_3N, CH_2Cl_2, (87%); (iv) H_2, Pd/C, EtOAc (98%); (v) NaN_3, DMF (87%); (vi) $HOCH_2CH_2OH$, PTSA, PhH (92%); (vii) TFA; (viii) K_2CO_3, $BrCH_2CO_2Et$, MeCN (64%, 2 steps); (ix) H_2, Pd/C, MeOH; (x) LiOH, H_2O; (xi) DPPA, Et_3N, DMF (40%, 3 steps); (xii) NaH, MeI, THF (73%) (xiii) LDA, **2**, THF, –78 °C (43%); (xiv) MsCl, Et_3N, CH_2Cl_2 then *t*-BuOK, THF, 0 °C (92%); (xv) AlH_3 (prepared from $LiAlH_4$ and $AlCl_3$), Et_2O then HCl (2 N), acetone (10–81%).

afford the [6,5]-spirocyclic core of **1** and this was readily achieved using an oxidative cleavage-aldol condensation sequence (Scheme 3). Although ozonolysis worked well on small scale, we found that the two-step dihydroxylation/periodate cleavage method was most suitable for large-scale synthesis of the keto-aldehyde **12**. A number of reaction conditions were screened for the key intramolecular aldol condensation reaction and we found that the use of phase-transfer conditions (tetrabutylammonium bromide, KOH–CH_2Cl_2) were particularly effective. Under these conditions we found that the cyclisation proceeded well to afford the desired cyclohexenone moiety, but significant amounts of the intermediate aldol product could also be isolated. In addition to facilitating cyclisation, the TBS-group was also removed from the protected secondary hydroxyl group under these conditions. Rather than being problematic, this deprotection proved to be an advantage as it eliminated a step later in the synthesis. It is interesting to note that the TBS-deprotection and aldol–cyclisation sequence could also be achieved if **12** was treated with TBAF (1 M in THF). Subsequent treatment of the mixture of products from the deprotection–aldol condensation with mesyl chloride and triethylamine resulted in the formation of the cyclohexenone **6** as the major new product (70–80% over 2 steps) and significant quantities of this material could be brought through this sequence of reactions.

In order to complete a synthesis of (–)-TAN1251A (**1**) we next reduced the cyclohexenone (H_2, Pd/C) and displaced the mesylate with sodium azide. Protection of the ketone as its ethylene glycol ketal gave the [6,5]-spirocycle **14**. Our next key objective was to synthesise the bridged bicyclic intermediate **4**, as this would represent a formal synthesis of (–)-TAN1251A (**1**). The synthesis of **4** from **14** was successfully achieved as follows: Deprotection of **14** with TFA–CH_2Cl_2, followed by alkylation of the resulting amine with ethyl bromoacetate and reduction of the azide (H_2, Pd/C, MeOH) afforded the amine **13**. As our own synthesis of **1** was progressing, Kawahara et al. published their second generation synthesis of **1**[2f] and they also proceeded via the amine **13**.[11] We were still keen to complete a synthesis of the bridged bicycle **4**, so we used the two-step route of Kawahara, which involved DPPA-mediated amide coupling to close the bicyclic ring system and alkylation of the amide-nitrogen with MeI–NaH. The synthesis of **4** represents a new formal synthesis of (–)-TAN1251A (**1**), but for the sake of completeness we achieved a total synthesis of **1** from **4** via the intermediate **15** following the route described previously in the literature.[2c,e,12]

In summary, we have successfully completed a synthesis of (–)-TAN1251A (**1**) starting from *trans*-4-hydroxyproline using an alkylidene carbene 1,5-CH insertion reaction as a key step. We have shown that the key [6,5]-spirocyclic amine **14** can be synthesised from the [5,5]-spirocycle **5** via an oxidative cleavage–aldol condensation sequence. Furthermore, the cyclohexenone **6** will provide the perfect platform from which we can study the enantioselective total synthesis of (+)-TAN1251B (**2**) via conversion of the enone into an α-hydroxy ketone.[6] The results of these studies will be reported in due course.

Acknowledgment

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(9) **Typical CH-Insertion Procedure:** KHMDS (0.5 M in PhMe, 127 mL, 63.4 mmol) was added to a stirring solution of **11** (12.8 g, 31.7 mmol) in dry Et_2O (200 mL) and the resulting mixture was stirred at r.t. for 1 h. The solvent was removed in vacuo and the residue was partitioned between brine (100 mL) and Et_2O (100 mL). The separated organic layer was dried ($MgSO_4$), concentrated in vacuo and purified by column chromatography [SiO_2, petrol (40–60 °C):Et_2O (10:1)] to give **5** as a colourless oil (10.7 g, 93%). $[\alpha]_D$ –61.5 (*c* 1.07, $CHCl_3$). ^1H NMR (400 MHz, DMSO-d_6, 100 °C): δ = 5.30 (br s, 1 H), 4.30 (app. quin., *J* = 4.5 Hz, 1 H), 3.55 (ddd, *J* = 11.2, 5.6, 0.8 Hz, 1 H), 3.20 (ddd, *J* = 11.2, 4.5, 1.2 Hz, 1 H), 2.40–2.13 (m, 3 H), 2.05 (dd, *J* = 12.7, 4.5 Hz, 1 H), 1.87–1.79 (m, 2 H), 1.70 (s, 3 H), 1.36 (s, 9 H), 0.90 (s, 9 H), 0.10 (s, 3 H), 0.10 (s, 3 H). HRMS: 368.2638 [MH^+] ($C_{20}H_{38}NO_3Si$ requires 368.2621). Anal. Calcd for $C_{20}H_{37}NO_3Si$: C, 65.4%; H, 10.2%; N, 3.8%. Found: C, 65.1%; H, 9.9%; N, 3.8%.

(10) Flash column chromatography over $AgNO_3$-impregnated SiO_2 allowed small amounts of the (*E*)-vinylbromide-**10** to be isolated as a single geometric isomer.

(11) Coincidentally, the spirocycle **14** was also a key intermediate on Kawahara's second generation route, although it was synthesised in a different manner. Our ^1H NMR, ^{13}C NMR, HRMS and CHN analysis data were identical to that reported by Kawahara[2f] $[\alpha]_D$ +9.1 (*c* 1.03, $CHCl_3$) (lit[2f] $[\alpha]_D$ +8.9 (*c* 0.99, $CHCl_3$).

(12) We found that the final reduction of **15** was capricious and that (–)-TAN1251A(**1**) was quite difficult to isolate in pure form. These difficulties have not previously been reported for this compound, but significant losses of material were incurred upon repeated chromatography.