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# Stereodivergent Synthesis of Pseudotabersonine Alkaloids

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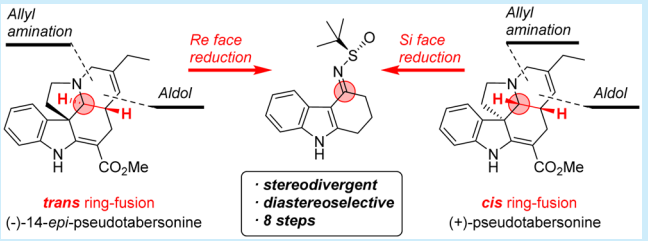
Supporting Information

**ABSTRACT:** An eight-step stereodivergent synthesis of enantiomerically pure (−)-14-epi-pseudotabersonine and (+)-pseudotabersonine has been developed from a common *N*-*tert*-butanesulfinyl ketimine key intermediate.




*Aspidosperma* alkaloids, a large family of monoterpenoid indole natural products,[1] have attracted considerable attention because of their diverse biological activities and the synthetic challenge associated with their complex polycyclic structure.[2] Most alkaloids of this class of natural products possess a pentacyclic core with a *cis*-junction between the C and D rings, as exemplified by the famous cancer chemotherapy medication vincristine (Figure 1). Among the plethora of *Aspidosperma*

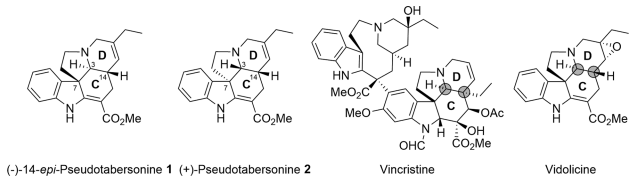



**Figure 1.** Representative *Aspidosperma* alkaloids.

alkaloids, only a few members bear *trans*-junction of the C and D rings, such as the recently isolated vidolicine (Figure 1).[3] *Trans* ring-fused pentacyclic analogs of natural *cis*-fused *Aspidosperma* alkaloids belong to apparently unexplored chemical space, which renders them highly attractive for applications in pharmaceutical research. Surprisingly, stereoselective synthesis of nonracemic *trans*-epimers of the *Aspidosperma* alkaloids is not reported in the literature as opposed to the large number of synthetic approaches toward enantiomerically pure natural products with *cis*-junction of the C and D rings.[4] Clearly, a stereoselective synthesis method to access both the *trans*- and the *cis*-fused pentacyclic systems in enantiomerically pure form is highly desirable.

After isolation from *Pandaca caducifolia* in 1975,[5] pseudotabersonine **2** has been targeted in a number of total syntheses.[6] However, only Stephenson succeeded in obtaining **2** in enantiomerically pure form.[6e] Racemic 14-*epi*-pseudotabersonine **1** has also been prepared;[7] however, stereoselective synthesis of nonracemic **1** has never been reported in the literature. Herein we report a stereodivergent synthesis of unnatural *trans* ring-fused (−)-14-*epi*-pseudotabersonine **1** and its *cis*-fused analog (+)-pseudotabersonine **2**, a member of the *Aspidosperma* alkaloids family. The synthesis of both (−)-**1** and (+)-**2** was accomplished from the common starting material possessing a *tert*-butanesulfinyl group (Ellman's chiral auxiliary).[8] The versatility of this diastereoselective synthetic approach may be highly valuable for further medicinal chemistry studies offering a structural diversity that could lead to a wider spectrum of biological activities.[9]

We envisioned three key retrosynthetic disconnections for the stereodivergent asymmetric synthesis of natural products (−)-**1** and (+)-**2** (Scheme 1). Specifically, ring D in tetracycles **3** and **4** would be formed by intramolecular allylic alkylation of the activated forms of *syn*- and *anti*-1,3-amino alcohols **5** and **6**. The C3 stereogenic centers (for numbering in **1** and **2**, see

**Scheme 1. Retrosynthetic Analysis of (−)-14-*epi*-Pseudotabersonine 1 and (+)-Pseudotabersonine 2**

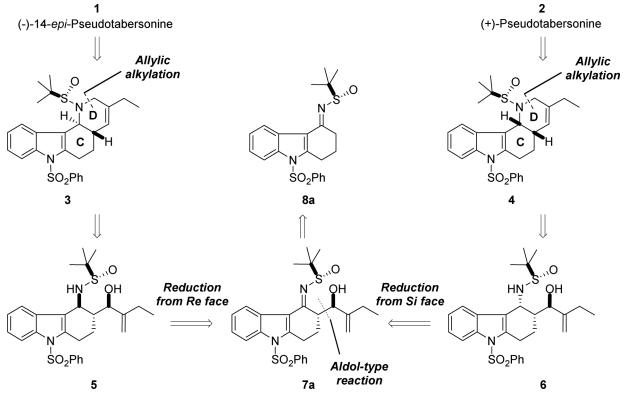



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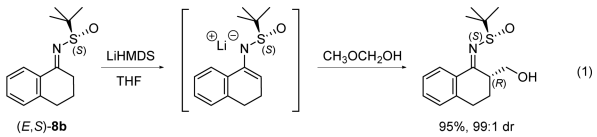
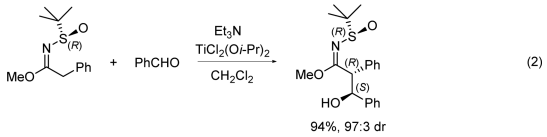
Figure 1) would be established by diastereoselective, and stereodivergent, reduction of (*S*)-*N*-*tert*-butanesulfinylketimine **7a**.[10] Furthermore, we envisioned that the Ellman's chiral auxiliary would also control the formation of the asymmetric C14 center in a diastereoselective aldol-type reaction between 2-ethylacrolein and (*S*)-*N*-*tert*-butanesulfinylketimine **8a**. Hence, Ellman's chiral auxiliary would direct the formation of both stereogenic C3 and C14 centers, thus providing access to both *cis*- and *trans*-fused pseudotabersonine alkaloids from a common intermediate **8a** (Scheme 1). Finally, the configuration at C7 will be controlled by the C3 stereogenic center during the conversion of tetracycles **3** and **4** into the targets **1** and **2** as described for *cis*-fused systems.[4j,7] (*S*)-*N*-*tert*-Butanesulfinylketimine **8a** was prepared in two steps from the commercially available 1,2,3,9-tetrahydro-4*H*-carbazol-4-one by an initial *N*-protection of the indole nitrogen, followed by condensation with (*S*)-*tert*-butanesulfinamide at 75 °C in the presence of $Ti(OEt)_4$ (75% over two steps; see Supporting Information (SI) for details).[11] Imine (*E*,*S*)-**8a** was obtained as a single *E* diastereomer; the *E* configuration of the imine was assigned based on X-ray crystallographic analysis of structurally closely related analogue (*E*,*S*)-**8k**.[12]

The diastereoselective aldol-type reaction of the imine (*E*,*S*)-**8a** with 2-ethylacrolein was next addressed. In a previous study, we have shown that the aldol-type reaction between lithium enamides of cyclic (*S*)-*N*-*tert*-butanesulfinylketimines (such as (*E*,*S*)-**8b**) and methoxymethanol (an easy-to-handle source of monomeric anhydrous formaldehyde) proceeds with excellent diastereocontrol (99:1 dr; eq 1).[12] We have also reported a




highly diastereoselective (up to 98:2 dr) aldol-type reaction of (*R*)-*tert*-butanesulfinylimidates with a range of nonenolizable aldehydes with excellent *syn*/*anti* selectivity (eq 2).[13] In the latter case, the use of a weak base $Et_3N$ in combination with $TiCl_2(O\text{-}i\text{Pr})_2$ was crucial to prevent the retro-aldol process. In both cases, a similar facial selectivity for the two aldol-type reactions was observed: aldehydes approach the opposite face of the bulky *tert*-butyl group of the Ellman's chiral auxiliary.

We envisioned that the titanium-based aldolization should also be amenable to the condensation of imine (*E*,*S*)-**8a** with 2-ethylacrolein. Indeed, we were pleased to find that the desired 1,3-iminoalcohol ($S_S$,*R*,*R*)-**7a** was readily formed in 85% yield, with excellent diastereoselectivity (99:1 dr) and complete *syn*/*anti* control (Figure 2). The scope of the reaction was examined with a range of cyclic *tert*-butanesulfinyl ketimines and a variety of nonenolizable aldehydes (Figure 2). Excellent levels of facial selectivity (>99:1 dr) were observed for the formation of all aldol products ($S_S$,*R*,*R*)-**7b**–**k**. Excellent *syn*/*anti* selectivities (up to 99:1 dr) were observed for the formation of aldol products ($S_S$,*R*,*R*)-**7b**–**h**,**j** from α-tetralone ketimine (*E*,*S*)-**8b**.[14] Structurally related ketimines (*E*,*S*)-**8i**,**j** afforded the corresponding aldolization products ($S_S$,*R*,*R*)-**7i**,**j** with slightly reduced *syn*/*anti* selectivity (94:6 dr). Indan-1-one-derived

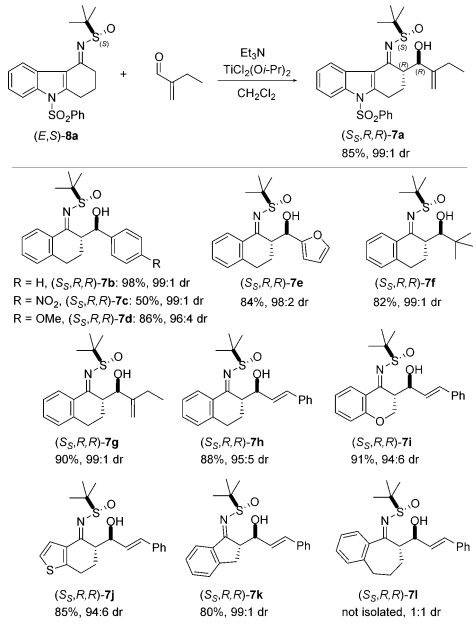



**Figure 2.** Diastereoselective aldol-type reaction.

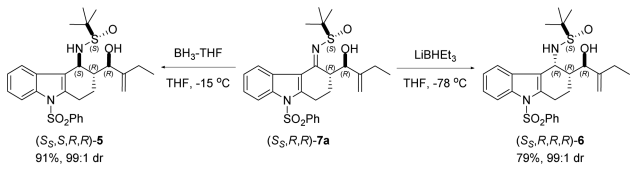
(*S*)-*tert*-butanesulfinyl ketimine (*E*,*S*)-**8k** underwent a highly diastereoselective (99:1 dr) reaction with cinnamaldehyde yielding ($S_S$,*R*,*R*)-**7k**, whereas the related benzosuberone ketimine (*E*,*S*)-**8l** reacted with poor *syn*/*anti* selectivity.[15] A range of nonenolizable aldehydes, such as aromatic ones, furfural, cinnamaldehyde, and pivalaldehyde, can be successfully engaged in this aldol-type reaction (Figure 2).

The relative *anti* configuration of the two newly created asymmetric carbons was determined by X-ray crystallographic analysis of aldol product ($S_S$,*R*,*R*)-**7g** (see SI). We have extrapolated the ($S_S$,*R*,*R*) relative configuration for all other aldol products (Figure 2). This configuration of the aldol products implies an approach of the aldehyde to the deprotonated (*S*)-*tert*-butanesulfinyl enamine intermediates from the opposite face to the bulky *tert*-butyl group, with a most probable cyclic transition state templated by titanium (for stereoinduction model see SI, p S26). The asymmetric induction for the aldol reaction of *tert*-butanesulfinyl ketimines (*E*,*S*)-**8a**–**k** is in full agreement with that observed earlier for *tert*-butanesulfinyl imidates.[13]

The stereodivergent synthesis of pseudotabersonine alkaloids **1** and **2** required a highly diastereoselective reduction of the three stereogenic-centers-containing *tert*-butanesulfinyl ketimine ($S_S$,*R*,*R*)-**7a**, either from the *Re* face (en route to target **1**) or from the *Si* face (for target **2**).

Importantly, Ellman has demonstrated that the reduction diastereoselectivity of the C=N bond in β-hydroxy-*N*-sulfinyl ketimines is controlled by the stereochemistry of the *tert*-butanesulfinyl group, with no influence of the β-alcohol.[16] Likewise, we have shown that the stereogenic center in the α-

**Scheme 2. Diastereoselective Reduction of Imine ($S_S$,*R*,*R*)-7a**



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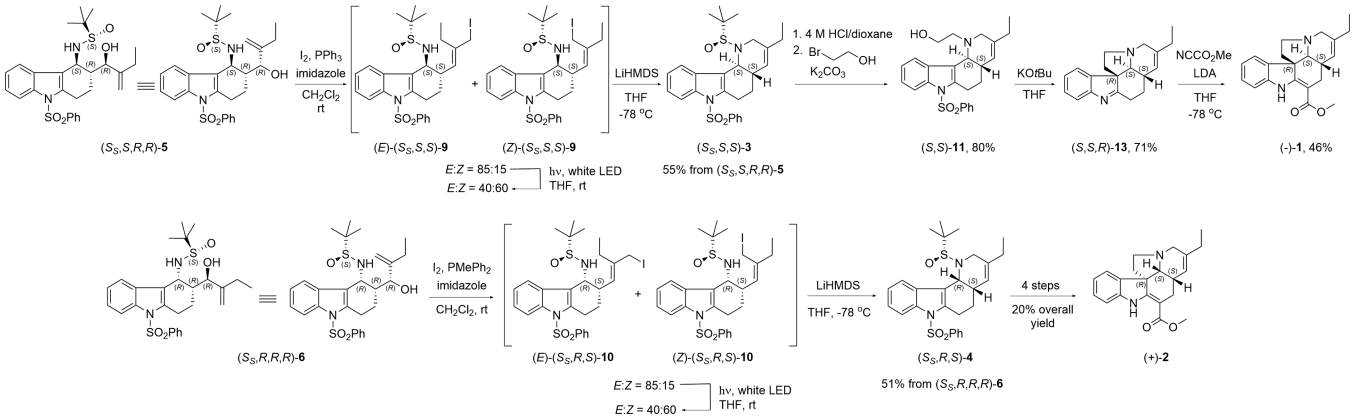
**Scheme 3. Synthesis of (−)-14-*epi*-Pseudotabersonine (−)-1 and (+)-Pseudotabersonine (+)-2**




position to the *tert*-butanesulfinyl ketimine moiety also does not influence diastereoselectivity of the reduction.[12] Hence, the diastereoselective reduction of the C═N bond would be controlled solely by the Ellman's chiral auxiliary. We envisioned that the formation of ($S_S$,*S*,*R*,*R*)-**5** would require a chelation-assisted delivery of hydride from the *Re* face, involving a complexation between the sulfinyl oxygen and a reducing agent.[17] Indeed, the reduction of the imine ($S_S$,*R*,*R*)-**7a** with $BH_3$−THF proceeded with excellent diastereoselectivity (99:1 dr; see Scheme 2) and afforded the desired *N*-sulfinyl amine ($S_S$,*S*,*R*,*R*)-**5**. Synthesis of the diastereomeric *N*-sulfinyl amine ($S_S$,*R*,*R*,*R*)-**6** apparently required the delivery of hydride on the less hindered *Si* face. This was achieved with excellent diastereoselectivity (99:1 dr) by using $LiBHEt_3$, a reducing agent that cannot coordinate to sulfinyl oxygen (Scheme 2). Hence, a proper choice of reducing agent selectively led to the formation of either configuration at C3 in a predictable way.

The formation of pseudotabersonine D ring by intramolecular allylic alkylation of enantiomerically pure 1,3-amino alcohols ($S_S$,*R*,*R*,*R*)-**5** and ($S_S$,*S*,*R*,*R*)-**6** was next addressed. Disappointingly, extensive screening of cyclization conditions such as intramolecular Pd-catalyzed (Tsuji−Trost) cyclization of allylic alcohols[18] or allylic acetates,[19] as well as intramolecular allylic amination in the presence of Brønsted or Lewis acids,[20] did not result in the cyclized product, from neither ($S_S$,*R*,*R*,*R*)-**5** nor ($S_S$,*S*,*R*,*R*)-**6**. Neither successful were attempts to effect the cyclization under Mitsunobu reaction conditions.[21]

To overcome this problem, we thought of an alternative strategy based on an initial allylic isomerization by an external nucleophile, which would act as a leaving group in a subsequent $S_N2$-type cyclization (see Scheme 3). We reasoned that the external nucleophile had to be (a) sufficiently reactive to effect an $S_N2'$-type allyl substitution; (b) bulky enough to react at the less hindered side of the allyl moiety ($S_N2'$ vs $S_N2$ substitution); and (c) serve as a good leaving group for a subsequent cyclization. After some experimentation, iodine was chosen as the external nucleophile. Iodide ($S_S$,*S*,*S*)-**9** was obtained as an inseparable 85:15 mixture of *E*/*Z* isomers from ($S_S$,*S*,*R*,*R*)-**5** under modified Appel conditions (see Scheme 3). Disappointingly, only the minor *Z*-isomer underwent the $S_N2$ cyclization affording the tetracyclic ($S_S$,*S*,*S*)-**3** (12% yield), leaving the major *E*-isomer unreacted. The latter could only partially be recovered as a result of its decomposition under the cyclization conditions.

An *E* to *Z* isomerization of double bond of allyl iodide ($S_S$,*S*,*S*)-**9** would solve the cyclization problem. It was ultimately found that the *E*/*Z* ratio could be reversed to 40:60 upon irradiation with visible LED light (1400 lm for 1 h at rt). Gratifyingly, the cyclization of the *Z*-enriched allyl iodide in the presence of LiHMDS afforded the *trans* ring-fused tetracycle ($S_S$,*S*,*S*)-**3** in 55% yield over two steps (Scheme 3). Unfortunately, prolonged irradiation with visible light failed to further increase the amount of the *Z*-isomer suggesting that the 40:60 ratio corresponds to thermodynamic equilibrium. An attempt to effect the light-mediated *E*/*Z* equilibration under the cyclization conditions (LiHMDS, −78 °C) failed: the isomerization did not proceed at −78 °C, whereas at −20 °C the *Z*-isomer underwent various side reactions.[22]

Tetracycle ($S_S$,*S*,*S*)-**3** was next elaborated into (−)-14-*epi*-pseudotabersonine **1** in a four-step sequence (Scheme 3). Cleavage of Ellman's chiral auxiliary was followed by alkylation with 2-bromoethanol to afford (*S*,*S*)-**11** (80% in two steps). Subsequent one-pot sequential *N*-deprotection/*O*-sulfonylation, followed by Bosch−Rubiralta spirocyclization[4j,7b,23] afforded pentacycle (*S*,*S*,*R*)-**13** in 71% yield. Finally, *C*-acylation of the lithium-enamide[24] of (*S*,*S*,*R*)-**13** using Mander's reagent[25] afforded enantiomerically pure (−)-**1** (46% yield).

(+)-Pseudotabersonine **2** was synthesized from 1,3-amino alcohol ($S_S$,*R*,*R*,*R*)-**6** using a similar sequence (Scheme 3). Notably, the synthesis of allyl iodide ($S_S$,*R*,*S*)-**10** required the use of the less bulky $Ph_2PMe$, instead of $Ph_3P$, in combination with iodine and imidazole for a more efficient transformation (51% compared to 15% with $PPh_3$). The less hindered $Ph_2PMe$ facilitates the Appel-type reaction of the more sterically hindered allylic alcohol ($S_S$,*R*,*R*,*R*)-**6** as compared to the less hindered ($S_S$,*S*,*R*,*R*)-**5** (Scheme 3). The following steps were effected without any modification, affording (+)-**2**. Analytical data for (+)-**2** (e.g., $^1H$ and $^{13}C$ NMR spectra, optical rotation) were in complete agreement with those reported in the literature.[5,7a]

In summary, a stereodivergent eight-step synthesis of enantiomerically pure (−)-14-*epi*-pseudotabersonine (10.5% overall yield) and (+)-pseudotabersonine (7.3% overall yield) has been developed from a common *N*-*tert*-butanesulfinyl-ketimine intermediate. The most notable steps are (1) a highly diastereoselective (99:1 dr) aldol-type reaction between *tert*-butanesulfinyl ketimine and 2-ethylacrolein, creating two adjacent stereogenic centers, and (2) diastereodivergent reduction of an intermediate *N*-*tert*-butanesulfinyl ketimine from either the *Re* face (for (−)-14-*epi*-pseudotabersonine) or from the *Si* face (for (+)-pseudotabersonine). This strategy secured the desired *cis*- or *trans*-fusion between C and D rings



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of enantiomerically pure pseudotabersonine alkaloids. The developed synthetic approach opens an avenue to previously underexplored chemical space around *Aspidosperma* alkaloids possessing *trans*-fused C/D rings.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02635.

Synthetic details; NMR data (PDF)
X-ray crystallographic data for ($S_S$,*R*,*R*)-**7g** (CIF)
X-ray crystallographic data for (*E*)-**16** (CIF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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(14) Equally high *syn*/*anti* selectivities were observed in the reaction of benzaldehyde with *tert*-butanesulfinyl ketimine (*E*,*S*)-**8b** (99:1 dr) and with the corresponding nonchiral *tert*-butanesulfonyl ketimine (*E*)-**15** (99:1 dr; see SI). In the latter case, the major diastereomer of racemic amino alcohol (*E*)-**16** was formed with *anti* configuration as evidenced by single crystal X-ray data (see SI).

(15) Exact *syn*/*anti* ratio for ($S_S$)-**7l** cannot be determined because of the concomitant formation of the corresponding dehydration product.

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