ORGANIC LETTERS

2011
Vol. 13, No. 21
5827–5829

An Approach to the Hexacyclic Skeleton of Trigonoliimines

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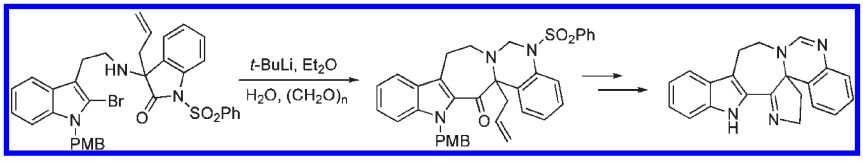
Received September 12, 2011

ABSTRACT



A strategy to construct the hexacyclic skeleton of trigonoliimines A, B and their derivatives involving a carbanion-triggered intramolecular cyclization of a seven-membered ring and a subsequent six-membered ring formation in one pot is described.

Trigonoliimines, a family of indole alkaloids, were first isolated by Hao and co-workers from the leaves of *Trigonostemon lii* collected in the Yunnan province of China in 2010 (Figure 1).[1] Trigonoliimine A (**1a**) and C (**2**) were tested for their bioactivity, and the former has been shown to possess anti-HIV activity (EC_{50} = 0.95 μg/mL). The unique ring structures of trigonoliimines along with their potential biological activity make them attractive targets for synthesis. During the course of our studies toward these molecules, Tambar,[2] Movassaghi,[3] and co-workers reported their elegant total synthesis of these molecules based on a biogenetic hypothesis.[1] Recently, a nice biomimetic construction of the trigonoliimine C skeleton was also reported by Hao and co-workers.[4] Herein we wish to report our synthetic approach to the hexacyclic skeleton of trigonoliimine A and B.

Our retrosynthetic analysis of the hexacyclic skeleton of trigonoliimines is illustrated in Scheme 1. Trigonoliimine skeleton **3** could originate from compound **4** via oxidation. The five-membered imine could be formed from **5** via an aza-Wittig reaction. The fused seven- and six-membered rings in **5** were envisioned to form from **6** via carbanion-triggered intramolecular opening of the protected amide and a subsequent formation of the hydropyrimidine ring. Compound **6** could be prepared from imine **7**, which could come from the coupling of tryptamine derivative **8** and commercially available isatin (**9**).

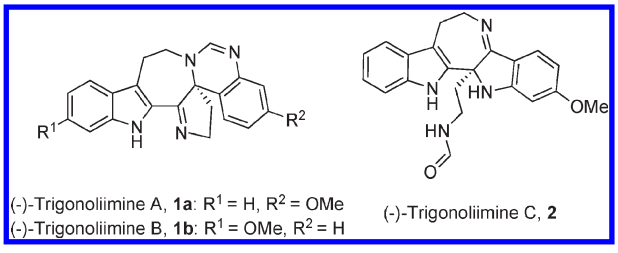


Figure 1. Structures of trigonoliimines.

The synthesis of intermediate **6** for the cyclization is outlined in Scheme 2. Readily available compound **10**[2,5]

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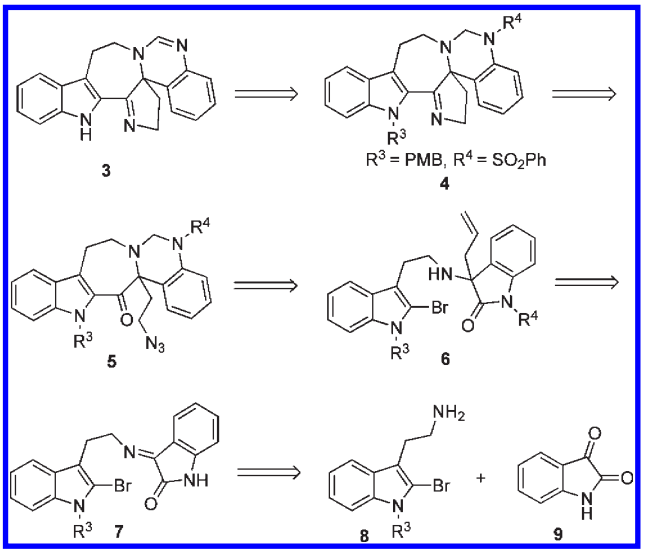
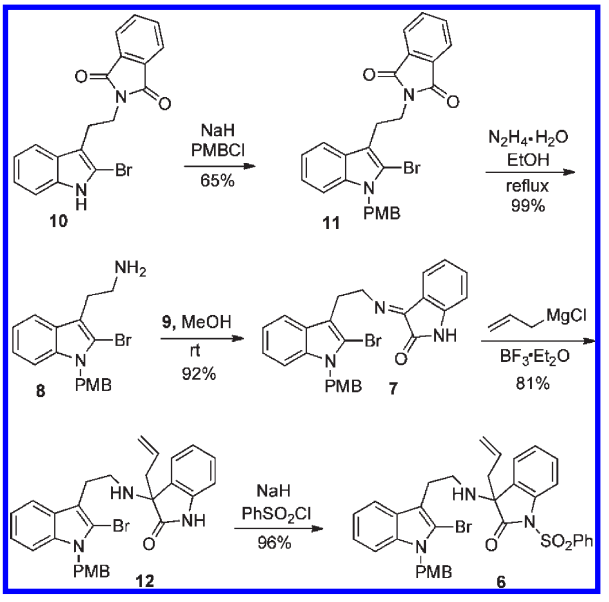
10.1021/ol202475r
Published on Web 10/11/2011

Scheme 1. Retrosynthetic Analysis of Trigonoliimine Core



Scheme 2. Synthesis of Compound **6**



was protected with PMB[6] to give compound **11** in 65% yield. Refluxing **11** with $N_2H_4{\bullet}H_2O$ in EtOH afforded amine **8** in 99% yield. Coupling **8** with isatin (**9**) in CH_3OH at room temperature provided imine **7** in 92% yield.[7] Imine **7** was subsequently allylated with allyl magnesium chloride in the presence of boron trifluoride to give compound **12** in 81% yield.[8] Protection of **12** with $PhSO_2Cl$ provided our key intermediate **6** in 96% yield on a multigram scale.

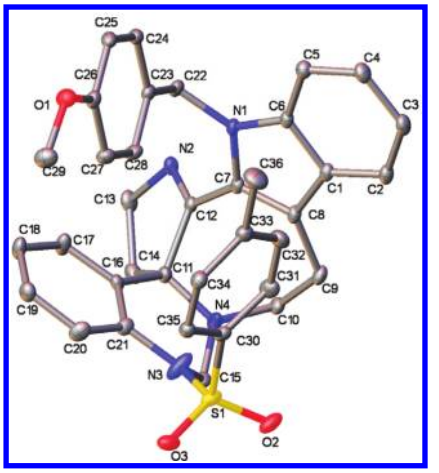


Figure 2. X-ray structure of compound **4b**.

The synthesis of trigonoliimine hexacyclic skeletons is shown in Schemes 3 and 4. Compound **13** was formed in 30% yield in one pot from compound **6** via bromide–lithium exchange, intramolecular nucleophilic acyl substitution to form the seven-membered ring,[9] and subsequent six-membered ring formation with paraformaldehyde.[10] Compound **13** was converted to azide **5** via oxidative cleavage of the vinyl group with $OsO_4/NaIO_4$ (85% yield),[11,12] reduction with $NaBH_3CN$[12] (78% yield), mesylation with MsCl, and azidation with NaN_3[13] (71% yield). Compound **4a** was readily formed from **5** in 88% yield via aza-Wittig reaction by refluxing with PPh_3 in toluene.[14] The hexacyclic skeleton was confirmed by the X-ray structure of its tosyl analogue **4b** (Figure 2).

The nitrogen-protecting group was found to be important for the key step (**6** to **13**, Scheme 3). For example, when the amide and the secondary amine were protected with the PMB or Boc group, no cyclization was observed.

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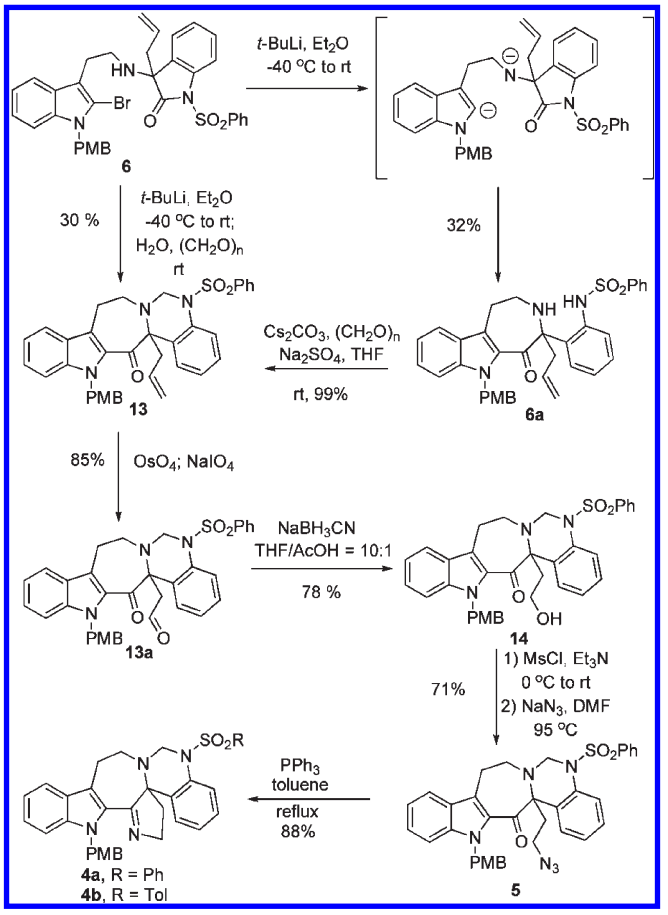
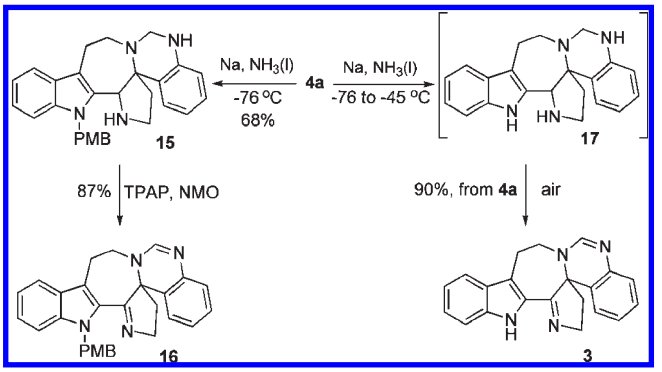
Scheme 3. Synthesis of Compound **4a**



When compound **12** was treated with CH_3SO_2Cl or $PhSO_2Cl$, only the amide was protected, leaving the secondary amine free. Neither the amide nor the secondary amine could be protected with NsCl under the conditions investigated. No cyclization was observed with the Ms protected compound. However, desired seven-membered ring compound **6a** was formed in 32% yield from **6** after much experimentation with various reaction conditions (Scheme 3). The cyclization was found to be sensitive to the solvent, temperature, and reaction time. The low yield for this step could be attributed to the side reactions. Attempts to isolate and identify the side products were not successful thus far. Compound **13** was obtained from **6a** in 99% yield (Scheme 3), indicating that the six-membered ring was formed efficiently and the seven-membered ring formation was the low-yield step.

The deprotection of **4a** was achieved with Na in liquid NH_3 (Scheme 4).[15] When the reaction was carried out at −76 °C, the benzenesulfonyl group was selectively removed to give compound **15** in 68% yield. Compound **15** was oxidized to imine **16** with TPAP/NMO in 87% yield.[16] When the deprotection of **4a** was carried out at −45 °C, both $PhSO_2$ and PMB groups were removed to give compound **17** as judged by the NMR of the crude product. Compound **17** was readily oxidized by air during column

Scheme 4. Syntheses of Compounds **3** and **16**



chromatography purification to give compound **3** in 90% overall yield. The hexacyclic skeleton of **3** was established by the X-ray structure (Figure 3).

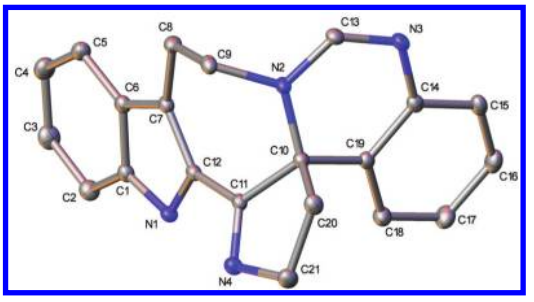


Figure 3. X-ray structure of compound **3**.

In summary, we have developed a new strategy to construct the hexacyclic skeleton of trigonoliimines A and B. The key step involves a carbanion-triggered intramolecular cyclization of a seven-membered ring and a subsequent tetrahydropyrimidine ring formation in one pot. The five-membered imine was formed via an aza-Wittig reaction. The dihydropyrimidine was readily formed via air oxidation. Further improvement of the synthetic sequence, the total syntheses of trigonoliimines A, B and their derivatives, and biological activity studies will be pursued.

Acknowledgment. The authors gratefully acknowledge the National Basic Research Program of China (973 program, 2011CB808600) and the Chinese Academy of Sciences for financial support.

Supporting Information Available. Experimental procedures, characterization data, and X-ray structures of **4b** and **3** along with NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.