ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Synthesis of the 10-Azatricyclo[3.3.2.0^{4,8}]decane Core of C_{20}-Diterpenoid Alkaloid Racemulsonine via Iodine(III) Promoted Transannular Aziridination Reaction

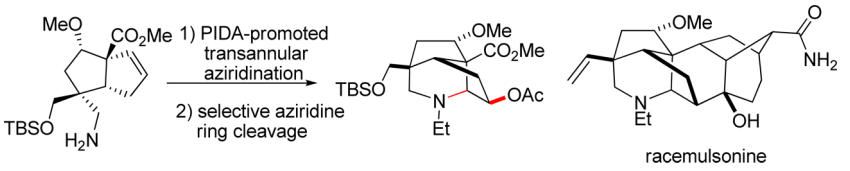
Ru-Huai Mei,† Zhi-Gang Liu,† Hang Cheng, Liang Xu,* and Feng-Peng Wang

Key Laboratory of Drug Targeting, Ministry of Education, and Department of Chemistry of Medicinal Natural Products, West China College of Pharmacy, Sichuan University, No. 17, Duan 3, Renmin Nan Road, Chengdu 610041, P. R. China

liangxu@scu.edu.cn

Received March 21, 2013

ABSTRACT



The functionalized A/E/F ring system of C_{20}-diterpenoid alkaloid racemulsonine has been efficiently synthesized. The Key steps involved a diastereoselective Au(I)-catalyzed annulation to form *cis*-fused cyclopentene and a PIDA promoted transannular aziridination of primary amine followed by regio- and stereoselective ring cleavage of bridged aziridine.

Aconitium species, commonly known as monkshood or wolf's bane, are the very famous plants that have been used extensively in traditional medicine throughout Asia and Europe as painkillers and produce various poisons and compounds of medicinal importance.[1] The fascinating bioactivities of these compounds are contributed by C_{18}-, C_{19}-, and C_{20}-diterpenoid alkaloids, which have long attracted scientists' strong interest in their phytochemistry, synthesis, and medicinal chemistry.[2] In 2000, our group reported the isolation of a structurally unique C_{20}-diterpenenoid alkaloid racemulsonine from *Aconitium racemulosum* var. *penzhounense*,[3] which represents the latest example of skeletal novelty of diterpenoid alkaloids generated by nature (Figure 1).[1d] This alkaloid shows an unprecedented hexacyclic ring framework containing a bridged A/E/F tricyclic subunit of 10-azatricyclo-[3.3.2.0^{4,8}]decane that features an unusual five-membered ring A, while all other naturally occurring diterpenoid alkaloids uniformly possess a six-membered ring A. Biogenetically, racemulsonine may be considered as the results of the sophisticated A-nor and B-homo-C-nor rearrangements of the known denudatine-type diterpenoids, one of the major groups of C_{20}-diterpenoids.[3]

Despite the intriguing biosynthetic and structural properties of the unique azahexacyclic skeleton, there was only a single report that described efforts to synthesize this compound, resulting in a useful methodology for the construction of an azatricyclic A/B/E-ring system bearing a bridged azabicyclo[3.2.1]octane subunit.[4] In combination with our extensive and long-standing interest in the chemistry of diterpenoid alkaloids,[5] and intrigued by the fascinating novel structural features and potential biological activities of this compound, we attempted to establish a methodology for the construction of a highly bridged

† These authors contributed equally.

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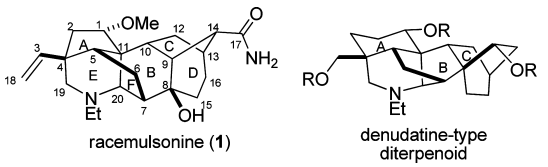
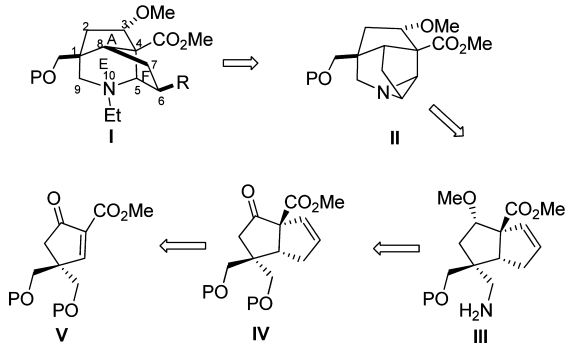


Figure 1. Structures of the hexacyclic diterpenoid alkaloids.

azatricyclic A/E/F-ring system **I**, which might serve as a crucial point for the total synthesis of racemulsonine. Herein, we report our endeavor to access the functionalized 10-azatricyclo[3.3.2.0^{4,8}]decane skeleton as one of the core bridged ring systems of racemulsonine through an intramolecular transanular aziridination followed by regio- and stereoselective aziridine ring cleavage.

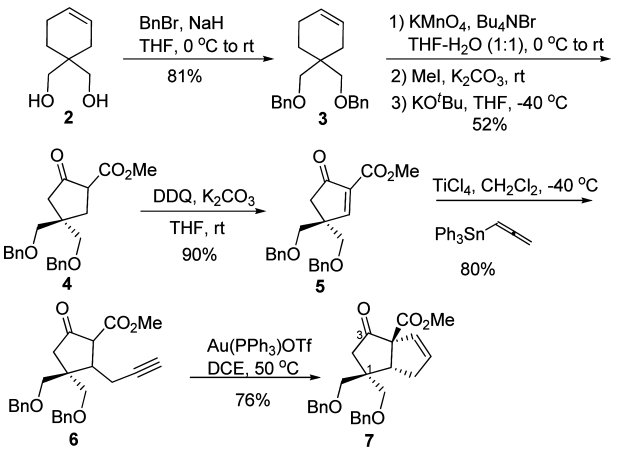
Our strategy toward the synthesis of the cage-like azatricyclic skeleton was attempted to utilize Nagata's intramolecular aziridination reaction[6] of unsaturated primary amine **III** to deliver a bridged aziridine **II** (Scheme 1), which could be expected to undergo a regio- and stereoselective aziridine ring cleavage to give **I**. The crucial unsaturated primary amine **III** could be prepared by facile founctional group interconversions from **IV**, which could arise from the α,β-unsaturated β-ketoester **V** followed by a known gold-catalyzed cyclopentene annulation procedure.[7]

Scheme 1. Retrosynthetic Analysis of Tricyclic Amine **I**



Our synthesis began with the protection of the known diol **2**[8] with a benzyl group (Scheme 2). According to the reported procedure for the methyl 4,4-bis(*tert*-butoxymethyl)-2-oxocyclopentane carboxylate,[8] dibenzyl oxide **3** was converted to β-ketoester **4** in three steps. Oxidation of **3** in aqueous $KMnO_4$ gave the corresponding diacid. After conversion of the diacid to the corresponding diester, Dieckmann cyclization of diester with potassium *tert*-butoxide in THF afforded the β-ketoester **4** in 52% overall yield. Oxidation of **4** with DDQ in THF gave the conjugated enone **5** smoothly.[9] Then the incorporation of a *cis*-fused cyclopentene onto the α,β-unsaturated β-ketoester **5** was next addressed via a two-step sequence. First, a conjugate propargylation of **5** with allenyltriphenylstannane in presence of $TiCl_4$ afforded the alkyne **6** in 80% yield;[10] subsequently, the Au(I) catalyzed annulation of **6** under the modified Toste conditions,[7] using 1,2-dichloroethane as the solvent at an elevated temperature (50 °C), proceeded efficiently to deliver the *cis*-fused cyclopentene **7** as a single diastereomer in 76% yield.

Scheme 2. Synthesis of Bicyclic A/F-Ring Precursor **7**



With the fused bicyclic A/F-ring precursor **7** in place, we then turned our attention to the installation of a methoxy group at C-3 and realization of the C-1 quaternary carbon center with the right configuration by desymmetrization of the prochiral diol (Scheme 3). Thus, exclusive reduction of the carbonyl group of **7** with $NaBH_4$ in methanol at −40 °C, followed by methylation with MeI/Ag_2O,[11] gave the C-1α methoxy product **8** as a single stereomer in 80% yield over two steps. The stereochemistry of **8** was assigned on the basis of NOE difference experiments which show through-space interactions between H-3 and H-8 (4.26 and 2.16 ppm). After selective removal of the benzyl groups of **8** by treatment with BBr_3 in dichloromethane, desymmetrization of the resulting 1,3-diol **9** was effected by treatment with TBSCl and imidazole in dicholomethane,[12] delivering

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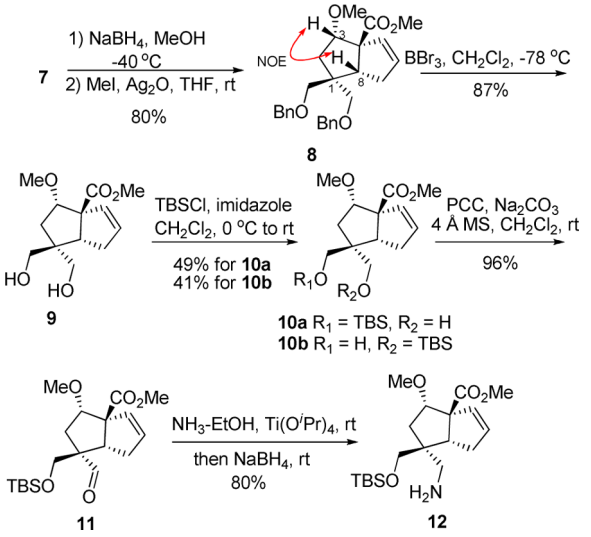
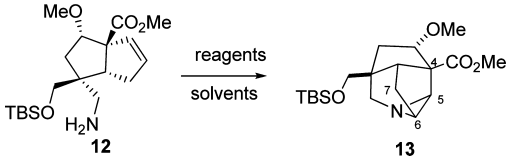
an easily separable mixture of TBS ether **10a** and **10b** in a 1.2:1 ratio and combined 90% yield. While the isomeric ratio is fairly low, the undesired minor isomer **10b** could be cleanly recycled to diol **9** by treatment with TBAF in THF, with minimal loss of material. The desired alcohol **10a** was then oxidized with PCC/Na_2CO_3 in dichloromethane to furnish a labile aldehyde **11**, which subsequently underwent a reductive amination by treatment with ammonia in ethanol and titanium(IV) isopropoxide, followed by reduction in situ with $NaBH_4$, affording the primary amine **12** in 80% yield.[13]

Scheme 3. Synthesis of Bicyclic Primary Amine **12**



With the key intermediate **12** in hand, our effort was focused on the synthesis of the challenging bridged aziridine. As shown in Table 1, an initial attempt to apply Nagata's intramolecular aziridination method[6,14] was carried out by oxidation of the primary amine **12** with excess $Pb(OAc)_4$ in benzene buffered with powdered K_2CO_3, providing the bridged aziridine **13** in a disappointing 15% isolated yield, along with 30% of recovered starting material and some unidentified low polar byproducts (entry 1). Further attempts using NCS[6] or NBS[15] as an oxidant as well as the modified procedure employing NCS and CuCl[16] were uniformly unsuccessful (entries 2–4). In light of some reported examples that oxidations of primary carbamate and *N*-amino phthalimide with hypervalent iodine reagents could generate nitrenoids capable of intermolecular or intramlecular aziridination of olefins,[17] we attempted to modify Nagata's method by employing iodine(III) reagents as oxidants. To our delight, when **12** was treated with phenyliodine(III) diacetate (PIDA) and K_2CO_3 in 1,2-dichloroethane at 55 °C for 1.5 h, **13** was obtained in an encouraging 33% yield with no starting material recovered (entry 5). After a series of experiments (entries 6–9),[18] we found that treatment of **12** with PIDA and K_2CO_3 using silica gel as an additive gave the best result, delivering **13** in up to 72% yield (entry 9). The use of iodosobenzene (PhIO) or the more potent oxidant phenyliodine(III) bistrifluoroacetate (PIFA) resulted in a lower yield (entries 10 and 11). This efficient intramolecular aziridination reaction proceeding *via* an iminoiodinane intermediate generated from a cycloalkenyl primary amine without a metal catalyst perhaps represents a new method to the bridged, polycyclic aziridine. It is noteworthy that the bridged aziridine **13** is quite stable and could be stored without decomposition in a refrigerator (0–4 °C) for more than two weeks even at neat liquid state.[6,14]

Table 1. Optimization of Reaction Conditions to Transform **12** into **13**



entry	reagents	solvent	*t* (°C)	time (h)	yield[a] (%)
1	$Pb(OAc)_4$, K_2CO_3	PhH	reflux	24	15[b,d]
2	NCS	CH_2Cl_2	rt	2	0[c,d]
3	NBS	CH_2Cl_2	rt	2	0[c,d]
4	NCS, CuCl	CH_2Cl_2	rt	2	0[c,d]
5	PIDA, K_2CO_3	DCE	55	1.5	33
6	PIDA, MgO	DCE	55	1.5	24
7	PIDA,$Cu(OTf)_2$	DCE	55	1.5	30
8	PIDA, $BF_3.Et_2O$	DCE	55	2	5
9	**PIDA, K_2CO_3, SiO_2**	**DCE**	**55**	**1**	**72**
10	PhIO, SiO_2	DCE	55	1	51
11	PIFA, K_2CO_3, SiO_2	DCE	55	1	48

[a] Isolated yields. [b] 30% of the amine **12** was recovered. [c] All of the amine **12** was consumed. [d] Unidentified low polar byproducts were observed.

Having achieved the synthesis of the bridged tetracyclic aziridine, the selective aziridine ring cleavage to prepare the desired A/E/F azatricyclic system was next investigated (Scheme 4). Gratifyingly, simple treatment of **12** with acetic anhydrate in CH_2Cl_2 at room temperature fortunately gave

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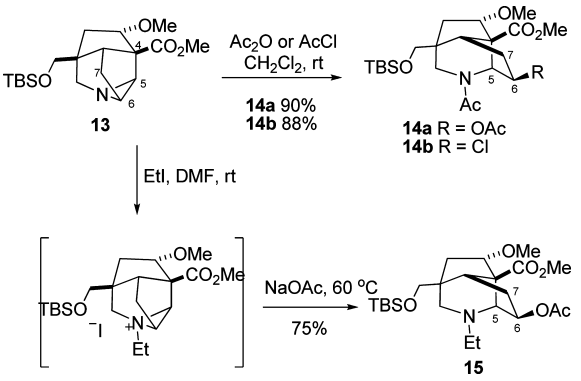
(18) For selected examples of Lewis acids facilitating the conversion of hypervalent iodine(III) reagents, see: (a) Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684. (b) Correa, A.; Tellitu, I.; Dominguez, E.; SanMartin, R. *J. Org. Chem.* **2006**, *71*, 8316. (c) Kita, Y.; Morimoto, K.; Ito, M.; Ogawa, C.; Goto, A.; Dohi, T. *J. Am. Chem. Soc.* **2009**, *131*, 1668.

Scheme 4. Synthesis of Azatricyclic A/E/F-rings **14** and **15**



the desired azatricyclo[3.3.2.0]decane compound **14a** as a single regio- and stereoisomer in excellent yield, despite that theoretically there might be another ring-opened regioisomer generated by nucleophilic attack at C-5 simultaneously . The high regioselectivity of this reaction might be attributed to the relatively more steric congestion at C-5 caused by the adjacent C-4 quaternary center. The ring-opened structure could be identified based on the ^{1}H NMR spectrum, which shows a double doublet (coupling with the vicinal two protons at C-7) at 4.78 ppm that could only be assigned to the proton at C-6 substituted with an OAc group.[19] The stereochemistry of the OAc group at C-6 was established as an *exo* orientation on the basis of the observation of the key NOESY relationship between H-6 and H-9 (Figure 2), which is compatible with an S_N2 nucleophilic attack of aziridine by acetate. Finally the whole stereochemical structure of **14a** was unequivocally confirmed based on the interpretation of its 2D NMR spectra (see Supporting Information). Furthermore, acetyl chloride was used to open the aziridine **13**, yielding the chlorine substituted tricyclic amide **14b** in 88% yield with

(19) The double doublet displayed by the signal of the proton at C-6 of **14a** at 4.78 ppm is due to the fact that the dihedral angel between H-6 and H-5 is *ca*. 90° based on observation of the molecular model of **14a**.

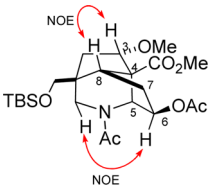


Figure 2. Key NOESY relationship of **14a**.

the same regio- and stereoslectivity. Direct introduction of the *N*-ethyl group to form the tricyclic amine was also investigated. Reaction of **13** with ethyl iodide in DMF at room temperarure produced an ethyl quaternary amine salt, which in turn was treated with sodium acetate in one pot at 60 °C, delivering *N*-ethyl azatricyclic amine **15** in 75% yield.

In summary, we have achieved the construction of the core bridged azatricyclic A/E/F-ring system of racemulsonine by using Au(I)-catalyzed annulation reaction and PIDA-promoted transannular aziridination of the primary amine followed by regio- and stereoselective ring cleavage as the key steps. The functionalized five-membered F-ring with an OAc or Cl substituent at C-6 and the methoxycarbonyl group at C-4 could be a good relay for further elaboration into the B-, C-, and D-rings of racemulsonine. These investigations are underway in our laboratory and will be published in due course.

Acknowledgment. Financial support for this work was provided by the National Natural Science Foundation of China (Nos. 30873147, 20902061, and 21272163).

Supporting Information Available. Experimental details, ^{1}H and ^{13}C NMR spectra for all new compounds, the NOE difference spectrum for compound **8**, 2D NMR spectra and their interpretations for compound **14a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.