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Total Synthesis of Pyrrolizidines 223H′, 239K′, 265H′, and 267H′ Found in Madagascan Frogs (*Mantella*) and Their Affinities for Nicotinic Acetylcholine Receptor

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Abstract—The total synthesis of pyrrolizidines 223H′, 239K′, 265H′, and 267H′ has been achieved starting from 1,5-hexadiene via a common synthetic intermediate **5**. The affinity of **1**–**4** for nicotinic acetylcholine receptor was evaluated.

Amphibian skin has provided a wide range of biologically active alkaloids. During the past 30 years, over 400 alkaloids of over 20 structural classes have been detected.[1] Recently, four 3,5-disubstituted pyrrolizidines 223H′, 239K′, 265H′, and 267H′ were isolated in Madagascan frogs (*Mantella*)[2]. Among them, it is known the relative structure of pyrrolizidine 223H′ is identical with that of xenovenine found in ant (*Solenopsis xenoveneum*).[3] So far, the syntheses of the xenovenine has been reported several times in chiral forms,[4] whereas the syntheses of the other three have never been reported in both racemic and chiral forms. Among the poison-dart frog alkaloids, 3,5-disubstituted, 5,8-disubstituted, and 5-substituted indolizidines[5] appear to represent an atypical and potent class of noncompetitive blockers for muscle-type and ganglionic nicotinic receptor-channels. However, the similar biological activity for homologues such as 3,5-disubstituted pyrrolizidines has not been investigated. Accordingly, we were stimulated into the development of a comprehensive synthetic program for these alkaloids. In this letter we communicate an asymmetric synthesis of 3,5-disubstituted pyrrolizidines 223H′, 239K′, 265H′, and 267H′ from trans-2,5-disubstituted pyrrolidine as a common synthetic intermediate available from 1,5-hexadiene together with their binding test for the nicotinic acetylcholine receptor (nAChR) (Chart 1).

A retrosynthetic plan is shown in Scheme 1. Namely, the stereoselective construction of 3,5-disubstituted pyrrolizidines could be achieved by the reductive annulation of a ketopyrrolidines II via transient iminium ions I.[4d] The pyrrolidines would be transformed from the common intermediate, *trans*-2-hydroxymethyl-5-(6-heptenyl)pyrrolidine (**5**), prepared by the kinetically controlled intramolecular amidomercuration[4d] of a chiral 4-pentenylcarbamate **6**, which would be obtained from achiral 1,5-hexadiene using the Sharpless asymmetric dihydroxylation (AD)[6] as chiral source.

The synthesis of the pyrrolidine **5** was carried out as shown in Scheme 2. The mono $(DHQD)_2$-PYR[7] ligand-induced AD reaction of 1,5-hexadiene (**7**) gave the dihydorxyolefin **8** in 64% yield (80% ee).[8] The olefin **8** was successively subjected to epoxidation,[9] and the regioselective cleavage of the resulting epoxide ring with 6-hexenylmagnesium bromide in combination with a cuprous iodide to give the alcohol **9** in 53% overall yield from **8**. The secondary alcohol was transformed by a four-step sequence (1. mesylation; 2. azidation; 3. reduction; 4. carbamation) into the desired *N*-benzyloxycarbonyl group (*N*-Cbz) **6**. The unsaturated carbamate underwent the cyclization mediated by mercuric acetate in THF followed by treatment with aqueous NaBr to afford the organomercurial, which was oxidatively demercuration to provide the trans diastereomer **5** in 63% yield without concomitant formation of the *cis* isomer and the azocine.

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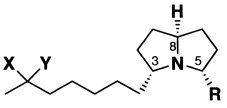
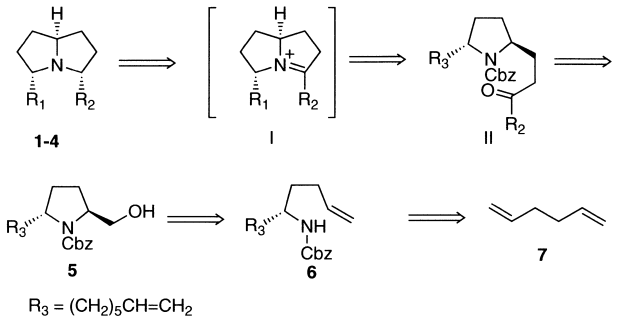
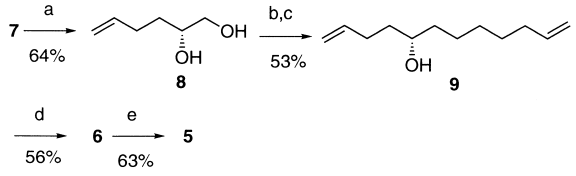


1 R = CH_3, X = Y = H pyrrolizidine 223H'
2 R = CH_3, X or Y = OH, Y or X = H pyrrolizidine 239K'
3 R = $CH_2CH_2CH_3$, X-Y = O pyrrolizidine 265H'
4 R = $CH_2CH_2CH_3$, X or Y = OH, Y or X = H pyrrolizidine 267H'

Chart 1.

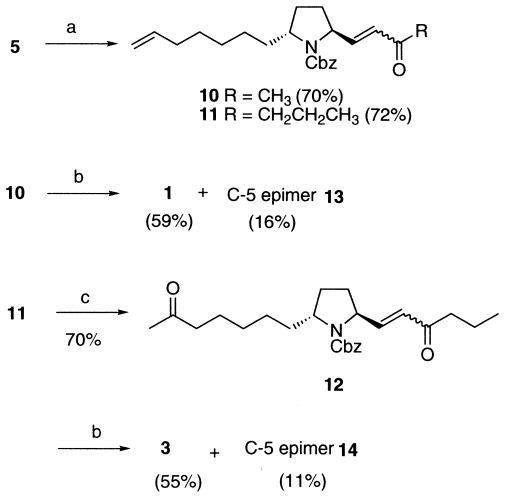


Scheme 1.



Scheme 2. (a) AD-mix-β [$(DHQD)_2$-PYR ligand]; (b) (1) $(CH_3O)_3CCH_3$/PPTS; (2) CH_3COBr/cat. Et_3N; (3) $K_2CO_3/CH_3OH/Et_2O$; (c) 6-hexenyllmagnesium bromide/CuI; (d) (1) MsCl/pyridine; (2) NaN3: (3) $LiAiH_4$; (4) $CbzCl/K_2CO_3$; (e) (1) $Hg(OAc)_2$/THF; (2) NaBr; (3) $NaBH_4/O_2$/DMF.

With the common synthetic intermediate **5** in hand, the elaboration of ring appendage (hydroxymethyl) was carried out. The Swern oxidation followed by the Horner–Emmons reaction using Masamune-Roush's condition gave the α,β-unsaturated ketons **10** and **11** in 70 and 72% yields, respectively. Exposure of **10** to hydrogen in the presence of $Pd(OH)_2$ as a catalyst in methanol provided the desired (−)-pyrrolizidine 223H′ **1** $[\alpha]_D^{26}$ −10.9 ($CHCl_3$), lit.[4d] $[\alpha]_D^{20}$ −11.6 ($CHCl_3$), in 59% yield along with its C-5 epimer **12** (16%). The spectral data of **1** were in agreement with those reported.[4] The Wacker oxidation of the terminal olefin on **11** followed by exposure of the resulting ketone to hydrogen in an above condition gave (-)-pyrrolizidines 265H′ **3** in 55% yield together with its C-5 epimer **14** (11%) (Scheme 3).

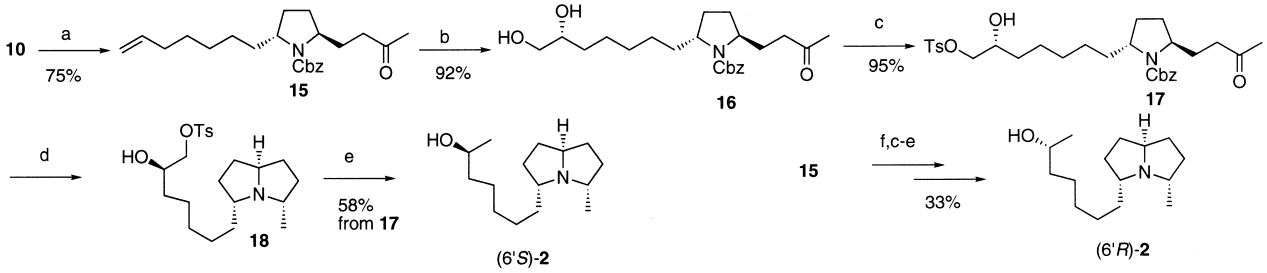


Scheme 3. (a) (1) $(COCl)_2$/DMSO/Et_3N; (2) $CH_3COCH_2PO(OCH_3)_2$/iPr_2EtN/LiCl or n-$C_3H_7COCH_2PO(OCH_3)_2$/iPr_2EtN/LiCl; (b) H_2/cat. $Pd(OH)_2$; (c) O_2/cat. $PdCl_2/CuCl/DMF/H_2O$.

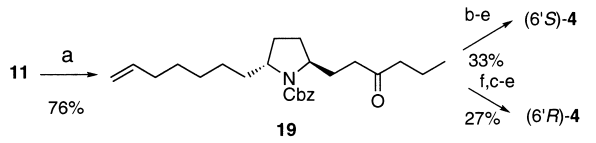
Next, we turned our attention to the synthesis of pyrrolizidines 239K′ **2** and 267H′ **4**. The installation of hydroxyl group of the C-3 appendage was performed by the AD reaction. Since the AD reaction of **10** gave a mixture of the diol and the tetraol, the reduction of conjugate olefin was carried out with Red-Al, in the presence of CuBr[10] to provide the monoolefin **15** in 75% yield. The $(DHQD)_2$-PYR[7] ligand-induced AD reaction of **15** afforded the diol **16** in 94% yield, of which selective monotosylation was performed with a two-step sequence (1. Bu_2SnO 2. *p*-TsCl) to give the tosylate **17** in 95% yield. Exposure of **17** to hydrogen in the presence of $Pd(OH)_2$ as a catalyst yield the pyrrolizidine **18**, which, without purification, was reduced with Super-Hydride®, to the desired pyrrolizidine 235H′ (−)-(6′*S*-hydroxy)-**2**[11] in 58% yield[12] from **17**. Similarly, (−)-(6′*R*)-**2**[11] was obtained from **15** via the $(DHQ)_2$-PYR[7] ligand-induced AD reaction of **15**[12] (Scheme 4).

Finally, two pyrrolizidines 267H′ (-)-(6′*S*)-and(-)-(6′*R*)-**4**[11,12] were prepared from **11** shown in Scheme 5.

With six chiral pyrrolizidines **1**–**4** in hand, our attention was directed toward their biologically activity. The interaction of the six pyrrolizidines **1**–**4** with binding sites on carbamylcholine-activated nicotinic acetylcholine receptor (nAChR) channel complex from *Torpedo californica* electric organ was investigated using radiolabeled probe, [^{3}H]-thienyl-cyclohexylpiperidine ([^{3}H]-



Scheme 4. (a) Red-A®/CuBr; (b) AD-mix-β [$(DHQD)_2$-PYR ligand; (c) (1) Bu_2SnO; (2) TsCl; (d) H_2/cat. $Pd(OH)_2$; (e) Super-Hydride®; (f) AD-mix-α [$(DHQ)_2$-PYR ligand].



Scheme 5. (a) Red-A®/CuBr; (b) AD-mix-β [$(DHQD)_2$-PYR ligand; (c) (1) Bu_2SnO; (2) TsCl; (d) H_2/cat. $Pd(OH)_2$; (e) Super-Hydride®; (f) AD-mix-α [$(DHQ)_2$-PYR ligand].

Table 1. Evaluation of the affinities of **1**–**4** for the nAChR of *Torpedo californica*[14]

Compounds	**1**	(6′*S*)-**2**	(6′*R*)-**2**	**3**	(6′*S*)-**4**	(6′*R*)-**4**	**20**	**21**
K_i, mM	0.05	3.3	8.3	0.83	3.1	3.1	0.42	0.37

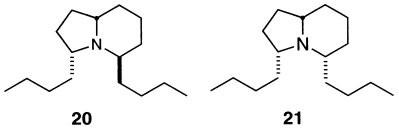


Chart 2.

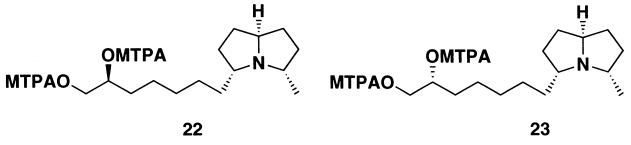


Chart 3.

TCP).[13] The K_i values for inhibition of [^{3}H]-TCP by **1**–**4**, compared to those of 3,5-disubstituted indolizidines **20** and **21**,[5a] are shown in Table 1. Interestingly, affinity of **1** was increased one order compared with those of the corresponding indolizidines. Since the introduction of a hydroxyl moiety in a side chain such as **2** and **4** remarkably decreases affinity, the structure–activity relationships suggest an important contribution of hydrophobic interactions. As a result, stereoconfiguration of hydroxyl had little effect on ion channel interactions (Chart 2).

In summary, the total synthesis of six 3,5-disubstituted pyrrolizidines **1**, (6′*S*)-**2**, (6′*R*)-**2**, **3**, (6′*S*)-**4**, and (6′*R*)-**4** has been asymmetrically achieved starting from a symmetrical 1,5-hexadiene. Their affinities for nAChR channel of *T. californica* were for the first time evaluated.

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11. The diastereomeric excess (de) of (6′*S*)-**2** and (6′*R*)-**2** was estimated to be 71 and 64% by ^{1}H NMR observation using bis-(+)-MTPA ester **22** and **23**, respectively. Similarly, the des of (6′*S*)- and (6′*R*)-**4** were estimated to be 73 and 68%, respectively, see Chart 3.
12. Although C-5 epimer of **4** may exist in a reaction mixture, we could not isolate that.
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14. Biological test method is referenced in 5c.