## Synthesis of All Diastereomers of the Piperidine—Alkaloid Substructure of Cyclopamine

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## ABSTRACT



All four diastereomers of the trisubstituted piperidine—alkaloids of the veratramine and jervine type were synthesized with complete stereocontrol starting from enantiopure citronellic acids. The flexible, high-yielding, and scalable route described here will facilitate convergent syntheses and give access to analogues of cyclopamine and other biologically active and diverse steroid alkaloids.

Cyclopamine (1) is the most prominent member of the biologically and structurally highly diverse family of *Veratrum* steroid alkaloids (Figure 1). Despite their *C*-nor-*D*-homo-[14(13 $\rightarrow$ 12)-*abeo*] carbon ring system, these natural products further possess characteristic trisubstituted piperidine substructures that are linked by a furan (jervine-type) or a carbon atom (veratramine-type) to the steroid skeleton.<sup>1</sup>

Especially cyclopamine as the first inhibitor of the Hedgehogsignaling pathway (Hh), which is of vital importance for both correct embryonic development and adult tissue homeostasis, has drawn a lot of attention in this decade.<sup>2</sup> Its first synthesis was recently accomplished by our group and proceeds in 20



Figure 1. Structure of cyclopamine and carbon numbering.

linear steps and 1% total yield from commercially available dehydroepiandrosterone (DHEA).<sup>3</sup> Since great demand exists for metabolically more stable and biologically more active analogues of cyclopamine, a convergent route to these compounds could be of high value.

<sup>(1)</sup> Li, H.-J.; Jiang, Y.; Li, P. Nat. Prod. Rep. 2006, 23, 735-752.

<sup>(2) (</sup>a) Lum, L.; Beachy, P. A. *Science* **2004**, *304*, 1755–1759. (b) Taipale, J.; Beachy, P. A. *Nature* **2001**, *411*, 349–354. (c) Taipale, J.; Chen, K. C.; Cooper, M. K.; Wang, B.; Mann, R. K.; Milenkovic, L.; Scott, M. P.; Beachy, P. A. *Nature* **2000**, *406*, 1005–1009.

We therefore developed an efficient and scalable route to all four diastereomers of the piperidine substructure of the *Veratrum* steroid alkaloids that can be used not only to access cyclopamine and analogues but also for the total synthesis of other members of this family.

The piperidine substructures of the *Veratrum* steroid alkaloids are substituted in position 2 with a two-carbon chain that will form *C*-20 and *C*-21 in the steroid alkaloid, a hydroxy group in position 3, that may be part of the furan (jervine-alkaloids) or be a free hydroxy group (veratramine-type) and a methyl group in position 5.

Three of the four possible diastereomers occur in natural products (see Figure 2). For the two most common diaste-



Figure 2. Structures, stereochemistry (steroid numbering), and occurrence in natural products of synthetic alkaloid precursors 2, 3, 4, and  $5^{.4-8}$ 

reomers (stereochemistry as in 2 and 4), the corresponding enantiomers can also be found. Only the *all-cis* diastereomer (stereochemistry as in 5) does not occur in nature. Since in compound 2 all substituents are placed equatorially, it is of no surprise that this stereochemistry is the most common and that the well-known natural products cyclopamine, veratramine, and jervine bear this structure.

A retrosynthetic analysis led us to define the order in which the three substituents should be introduced to the piperidine nucleus. Since the methyl group in position 5 was thought to be of no influence to the generation of the remaining stereocenters in 2- and 3-position, it could be placed in the beginning. The hydroxy group in the 3-position could (after its diastereoselective introduction) be utilized as an element of control for the attachment of the carbon substituent in the 2-position. As starting material, a carbon building block with a chiral methyl substituent was needed that, in addition, should be available in both enantiomeric forms. This task was fulfilled by the enantiopure citronellic acids.

Although both enantiomers of citronellic acid are commercially available, it was found more suitable to synthesize these compounds from cheaper materials. While (-)-(S)-citronellic acid (-)-**6** was accessible by oxidation of (-)-(S)-citronellal using silveroxide, (+)-(R)-citronellic acid was synthesized from (+)-(R)-pulegone by known procedures.<sup>9,10</sup> The chiral valerolactames could then be accessed in three steps and 75% total yield.<sup>11</sup> Starting with a Curtius rearrangement of the carboxylic acid (-)-**6** or (+)-**6** to the corresponding benzyl-carbamate (-)-**7** or (+)-**7**, and then an osmium(VIII)-catalyzed oxidative cleavage of the double bond,<sup>12</sup> these reactions already afforded the cyclic lactamoles, which in turn were oxidized to the lactames (-)-**8** and (+)-**8**, respectively, using Ley's TPAP/NMO (tetrapropylammonium perrhutenate/4-methyl-morpholine-4-oxide) system.

With both enantiopure protected lactames in hand, we searched for a way to introduce the hydroxy group diastereoselectively. Finally, the treatment of the lithium enolates with 8,8-dichlorocamphoryl-sulfonyl oxaziridine (DCCSO, commercially available in both enantiomeric forms or easily prepared from the camphorsulfonic acids<sup>13</sup>) proved to be ideal. Under optimized conditions, these reactions proceeded with complete diastereocontrol and a yield of 83–89% that already includes the subsequent protection as a pivaloate. These reactions were routinely conducted on the 10 g scale. The use of (+)-DCCSO gave rise to the 23-(*S*)-stereochemistry (as in (-)-10), and (-)-DCCSO yielded the 23-(*R*)-diastereomer, e.g. (+)-9 (Scheme 1). The orientation of the

Scheme 1. Synthesis of the Hydroxylated Lactames 9 and 10



methyl group had no influence on the stereochemical outcome.<sup>14</sup>

To introduce the remaining stereocenter for once in a transfashion with regard to the adjacent hydroxy group, the addition of a carbon nucleophile was envisioned. A quantitative yield with complete stereocontrol could be gained by the reaction of the corresponding acetate and a stabilized

<sup>(3)</sup> Giannis, A.; Heretsch, P.; Sarli, V.; Stöβel, A. Angew. Chem. 2009, 121, 8052–8055; Angew. Chem., Int. Ed. 2009, 48, 7911–7914.

<sup>(4)</sup> Mimaki, Y.; Sashida, Y. Chem. Pharm. Bull. 1990, 38, 1090–1092.
(5) Usubillaga, A. Phytochemistry 1988, 27, 3031–3032.

silylenol ether.<sup>15</sup> Therefore the protected hydroxylactames were reduced with superhydride and directly converted to the acetates (mixture of epimers) with Ac<sub>2</sub>O. Treatment of the latter with ethyl-3-phenyl-3-trimethylsiloxy-acrylate (**21**, see Supporting Information) under Sc(OTf)<sub>3</sub> catalysis proceeded smoothly and afforded **11** (Scheme 2). Cleavage of



the benzoyl moiety was affected by a retro-Claisen reaction using LiOH, and deprotection of the hydroxy group and the carboxylic acid gave the seco-acid which was immediately cyclized with EDC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide) to give the five-membered lactones 2 and 3, respectively (63–59% yield over five steps). From both 2and 3, several grams were prepared using this sequence.

A syn-addition to C-2 was achieved by the following sequence: Methylenation using the Petasis conditions<sup>16</sup> and subsequent hydroboration/oxidation gave the regioisomeric alcohols 13 and 14 with complete stereocontrol. The occurrence of 14 in this reaction must be attributed to a pivaloyl shift. Both compounds 13 and 14 were converted to the benzyl-protected diol 15 using standard protecting group manipulations.

Further elaboration into 4 was carried out by oxidation using the Dess-Martin-periodinane (DMP), Grignard reaction with methylmagnesium bromide, and again oxidation of the epimeric alcohols with DMP to yield the methylketone 4 as the only product. These transformations proceeded in a total yield of 15% over seven or nine steps, respectively. Starting from (-)-9 the *all-cis* substituted methylketone 5 could be accessed in the same way but with only minute amounts of pivaloyl-shifted material to be produced during the hydroboration/oxidation reaction, in a total yield of 23% over nine steps (Scheme 3).





In conclusion, any enantiomer of any diastereomer of the trisubstituted piperidine—alkaloid substructures of cyclopamine and all other jervine- and veratramine—steroid alkaloids can be obtained from readily available enantiopure citronellic acids by the two general routes described above, choosing either (+)-DCCSO or (-)-DCCSO in the hydroxylation step. Hence complete control of stereochemistry of the three substituents was demonstrated. Furthermore, all transformations proceeded in high yield and were shown to be scalable up to multigram quantities. We are therefore confident that implementation of this route will open access to new analogues and total syntheses of this interesting class of natural products.

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**Supporting Information Available:** Experimental procedures, compound characterization, and <sup>1</sup>H NMR and <sup>13</sup>C NMR data for all compounds. 2D-NMR spectral data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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<sup>(6) (</sup>a) Jiang, Y.; Li, H.; Li, P.; Cai, Z.; Ye, W. J. Nat. Prod. **2005**, 68, 264–267. (b) Jiang, Y.; Li, P.; Li, H.-J.; Yu, H. Steroids **2006**, 71, 843–848. (c) Li, H.-J.; Jiang, Y.; Li, P.; Ye, W.-C. Chem. Pharm. Bull. **2006**, 54, 722–724.

<sup>(7)</sup> Qian, Z.-Z.; Nohara, T. Phytochemistry 1995, 40, 979–981.

<sup>(8)</sup> Zhang, J. X.; Lao, A. N.; Xu, R. S. Chin. J. Org. Chem. 1994, 14, 289–292.

<sup>(9)</sup> Hashimoto, S.-I.; Yamada, S.-I.; Koga, K. Chem. Pharm. Bull. 1979, 27, 771–782.

<sup>(10)</sup> Overberger, C. G.; Weise, J. K. J. Am. Chem. Soc. 1968, 90, 3525–3532.

<sup>(11)</sup> This access is both shorter and more efficient than a seminal work by Woodward et al. dealing with the assignment of the absolute stereochemistry of the *Veratrum* alkaloids: Jeger, O.; Prelog, V.; Sundt, E.; Woodward, R. B. *Helv. Chim. Acta* **1954**, *37*, 2302–2306.

<sup>(12)</sup> Yu, W.; Mei, Y.; Kang, Y.; Hua, Z.; Jin, Z. Org. Lett. 2004, 6, 3217–3219.

<sup>(13)</sup> Chen, B.-C.; Murphy, C. K.; Kumar, A.; Thimma Reddy, R.; Clark, C.; Zhou, P.; Lewis, B. M.; Gala, D.; Mergelsberg, I.; Scherer, D.; Buckley, J.; DiBenedetto, D.; Davis, F. A. *Org. Synth.* **1996**, *73*, 159–167.

<sup>(14)</sup> A chemoenzymatic approach described by Willis et al. is both more tedious and of lower total yield and gives in addition only access to products with stereochemistry resembling that of (-)-9 and (-)-10: Crosby, S.; Hateley, M. J.; Willis, C. L. *Tetrahedron Lett.* 2000, 41, 397–401.

<sup>(15)</sup> Okitsu, O.; Suzuki, R.; Kobayashi, S. J. Org. Chem. 2001, 66, 809–823.

<sup>(16)</sup> Petasis, N. A.; Bzowej, E. I. J. Am. Chem. Soc. 1990, 112, 6392-6394.