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Enantiodivergent Synthesis of Both Enantiomers of Marine Alkaloids Haliclorensin and Isohaliclorensin, a Constituent of Halitulin†

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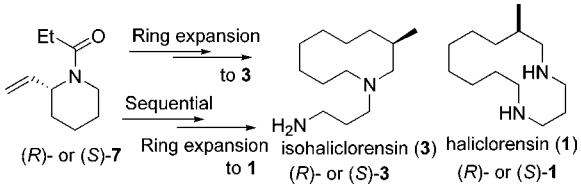
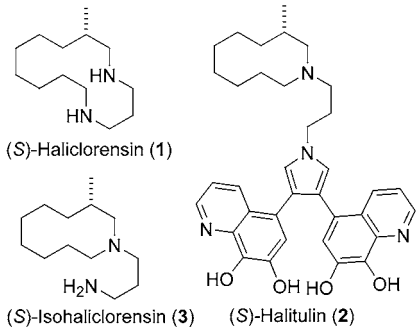
ABSTRACT



Starting from (3*R*)-5-benzotriazolyl-3-phenylperhydropyrido[2,1-*b*][1,3]oxazole 9, the enantiodivergent syntheses of both enantiomers of the marine alkaloids haliclorensin 1 and isohaliclorensin 3 have been achieved. Our syntheses feature ring-expansion reactions for the formation of the aza-macrocycle ring system of 3 and sequential ring-expansion reactions (aza-Claisen rearrangement and Zip reaction) for the formation of the aza-macrocycle ring system of 1.

Haliclorensin (**1**)[1] and halitulin (**2**)[2] are two unique alkaloids isolated from the marine sponge *Haliclona tulearensis*, which was collected in Sodwana Bay, Durban, South Africa. The strong cytotoxicity of haliclorensin against P-388 mouse leukemia cells and that of halitulin against several tumor cell lines have stimulated studies toward the total syntheses of both molecules. Steglich[3] and Banwell's[4] syntheses of haliclorensin allowed the revision of its structure to (−)-(*S*)-**1**,[3] and the initially assigned structure (**3**) for haliclorensin was subsequently renamed isohaliclorensin.[3] A recent report[5] on the first total synthesis of halitulin also confirmed the previously assigned structure (**2**) and allowed determination of its absolute configuration (15*S*).



Retrosynthetic analysis of **1** and **3** suggested **4** as a common precursor (Scheme 1). We envisioned forming the ring system of haliclorensin **1** via a ring expansion reaction[8] on the amino-lactam derived from **4**, and this, in turn, could potentially be derived from **6**. The latter could itself be accessed from **7** by an aza-Claisen rearrangement,[9,10] and **7**

† Dedicated to Professor Dr. Khi-Rui Tsai on the occasion of his 90th birthday.

(1) Koren-Goldshlager, G.; Kashman, Y.; Schleyer, M. *J. Nat. Prod.* **1998**, *61*, 282.
(2) Kashman, Y.; Koren-Goldshlager, G.; Gravalos, M. D. G.; Schleyer, M. *Tetrahedron Lett.* **1999**, *40*, 997.
(3) (a) Heinrich, M. R.; Steglich, W. *Tetrahedron Lett.* **2001**, *42*, 3287. (b) Heinrich, M. R.; Kashman, Y.; Spiteller, P.; Steglich, W. *Tetrahedron* **2001**, *57*, 9973.
(4) Banwell, M. G.; Bray, A. M.; Edwards, A. J.; Wong, D. J. *New J. Chem.* **2001**, *25*, 1347.
(5) Heinrich, M. R.; Steglich, W.; Banwell, M. G.; Kashman, Y. *Tetrahedron* **2003**, *59*, 9239.

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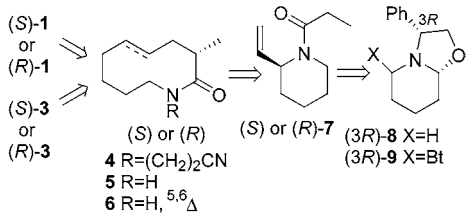
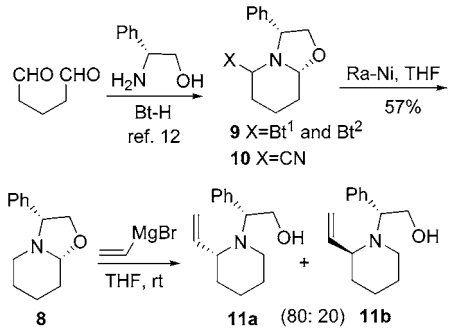
Scheme 1



could possibly be prepared from Husson's oxazolopiperidine **8**[11] or from Katritsky's benzotriazolyl oxazolopiperidine **9**[12] (Scheme 1).

As shown in Scheme 2, we started the synthesis of **11a**

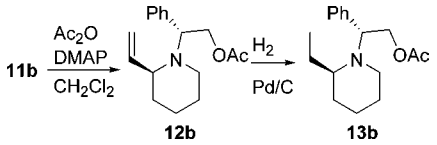
Scheme 2



and **11b** by condensing (*R*)-phenylglycinol with glutaraldehyde and benzotriazole[11,12] to obtain **9** as a regio- (Bt^1 and Bt^2) and diastereomeric mixture in high yield (Scheme 2). To convert **9** to **8**, a chemoselective reductive debenzotriazolation was required. We attempted Husson's conditions, namely, Raney nickel in refluxing THF for 20 h.[11a] However, this led to complex mixtures of products. Fortunately, when **9** was treated with an excess of freshly prepared Raney-Ni at room temperature for 7∼8 h, **8**[11a] was obtained as a 9:1 diastereomeric mixture in 57% yield.

With compound **8** in hand, we proceeded to study the nucleophilic alkylation of **8**. Although the ring opening of oxazolidines by Grignard reagents is a well-known procedure,[11−13] little was known about the stereochemical behavior of simple bicyclic oxazolidines such as **8**[14,15] in this type of reaction. Treatment of **8** with 4 molar equiv of vinylmagnesium bromide led to the vinylated products **11a**/**11b** in 80:20 ratio. The two diastereomers were separable by column chromatography. To determine the stereochemistry of the major diastereomer **11a**, the acetate **12b**, prepared from **11b**, was hydrogenated to give a known piperidine **13b** (Scheme 3).[16] Comparing the spectral data and optical

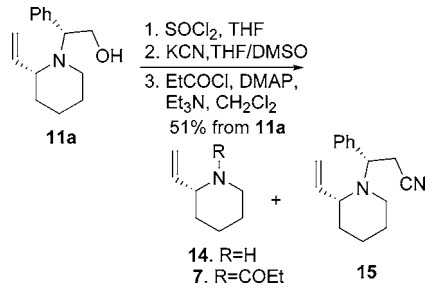
Scheme 3



rotation value of **13b** {$[\alpha]^{20}_D$ −65.1 (*c* 2.0, $CHCl_3$)} with those reported {lit.[16b] $[\alpha]^{23}_D$ −65.2 (*c* 2.3, $CHCl_3$) for the (2*R*,2′*R*)-enantiomer} allowed us to determine its absolute configuration as 2*R*,2′*R*. Thus, the absolute configuration of **11b** was 2*S*,2′*R*, and that of **11a** was 2*R*,2′*R*.

Removal of the benzylic chiral auxiliary from **11a**, without also affecting the vinyl group, was not a trivial task. Agami's nonreductive procedure[17] was adopted for this purpose. Thus, stirring a thionyl chloride solution of alcohol **11a** at room temperature for 1.5 h, followed by treatment of the resulting chloride with KCN in DMSO−THF, furnished, in one pot, the desired 2-vinylpiperidine (*R*)-**14**. The crude (*R*)-**14**, without purification, was allowed to react with propionyl chloride (Scheme 4). In this way, (*R*)-*N*-propionyl-2-vinyl-

Scheme 4



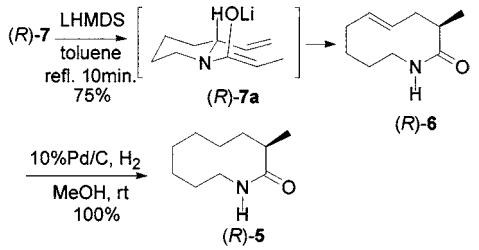
piperidine (**7**) {$[\alpha]^{20}_D$ +53 (*c* 1.1, $CHCl_3$)} was obtained in an overall yield of 51% from **11a**. The intermediate **15** was also isolated in a yield of 10%.

We next addressed the key ring expansion reaction. When a toluene solution of **7** was heated in the presence of LHMDS

(6) Banwell, M. G.; Bray, A. M.; Edwards, A. J.; Wong, D. J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1340.
(7) Usuki, Y.; Hirakawa, H.; Goto, K.; Iio, H. *Tetrahedron: Asymmetry* **2001**, *12*, 3293.
(8) For a treatise on the ring-enlarging reactions, see: Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH Publishers: New York, 1991.
(9) (a) Suh, Y. G.; Lee, J. Y.; Kim, S. A.; Jung, J. K. *Synth. Commun.* **1996**, *26*, 1675. (b) For an enantioselective aza-Claisen rearrangement of an analogue of **8**, see: Suh, Y. G.; Kim, S. A.; Jung, J. K.; Shin, D. Y.; Min, K. A.; Koo, B. A.; Kim, H. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3545.
(10) For related ring expansion reactions, see: (a) Edstrom, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 6690. (b) Diederich, M.; Nubbemeyer, U. *Angew. Chem., Int. Ed.* **1996**, *35*, 1026. (c) Sudau, A.; Nubbemeyer, U. *Angew. Chem., Int. Ed.* **1998**, *37*, 1141. (d) Sudau, A.; Munch, W.; Unbbemeyer, U. *J. Org. Chem.* **2000**, *65*, 1710.
(11) (a) Francolis, D.; Poupon, E.; Lallemand, M. C.; Kunesch, N.; Husson, H.-P. *J. Org. Chem.* **2000**, *65*, 3209. (b) Poupon, E.; Kunesch, N.; Husson, H.-P. *Angew. Chem., Int. Ed.* **2000**, *39*, 1493.
(12) Katritzky, A. R.; Qiu, G.; Yang, B.; Steel, P. J. *J. Org. Chem.* **1998**, *63*, 6699.
(13) For a review, see: Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383.
(14) Poerwono, H.; Higashiyama, K.; Yamauchi, T.; Kubo, H.; Ohmiya, S.; Takahashi, H. *Tetrahedron* **1998**, *54*, 13955 and refs cited therein.
(15) For the nucleophilic alkylation of a related ring system, see: (a) Yamazaki, N.; Kibayashi, C. *Tetrahedron Lett.* **1997**, *38*, 4623. (b) Pandey, G.; Das, P. *Tetrahedron Lett.* **1997**, *38*, 9073.

for 10 min, the enolate **7a** was generated and the desired aza-Claisen rearrangement[9a] took place, leading to the formation of (−)-azacyclodec-5-en-2-one **6** {white solid, mp 148−149 °C, $[\alpha]_D^{20}$ −48.8 (*c* 1.0, $CHCl_3$)} in a yield of 75% (Scheme 5). Since we had predicted that the aza-Claisen

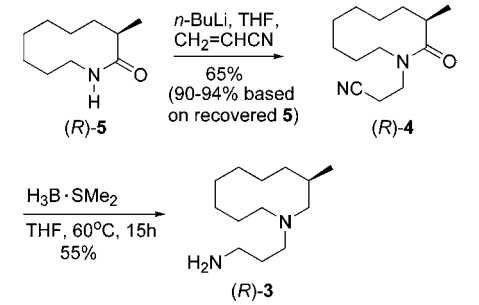
Scheme 5



rearrangement would proceed via the conformer **7a**,[9a] this would establish an (*R*)-configuration in **6**. The (*R*)-stereochemistry was confirmed by our synthesis of both (*R*)-isohaliclorensin (**3**) and (*R*)-haliclorensin (**1**) (vide infra). Saturation of olefinic double bond in **6** (H_2, 10%Pd/C, MeOH) furnished (+)-azacyclodecan-2-one **5** {white solid, mp 152−154 °C, $[\alpha]_D^{20}$ +20.3 (*c* 1.0, $CHCl_3$)} in quantitative yield.

Treatment of lactam **5** with a catalytic amount of *n*-butyllithium at −78 °C followed by addition of acrylonitrile led to the addition product **4** {$[\alpha]_D^{20}$ −59.2 (*c* 1.05, $CHCl_3$); yield 65%} along with recovered starting material **5** (33%) (Scheme 6). Finally, reduction of both the amide carbonyl

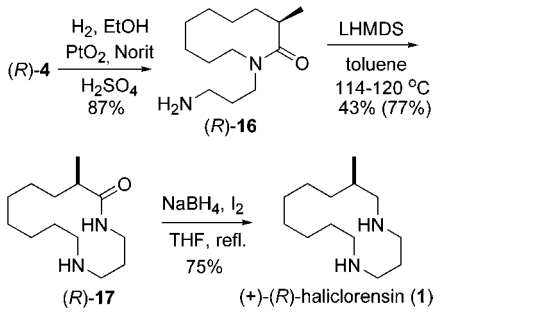
Scheme 6



and the cyano groups of **4** with an excess of borane dimethyl sulfide complex at 60 °C for 15 h provided isohaliclorensin (**3**) in 55% yield. Comparing the specific optical rotation of our synthetic isohaliclorensin (**3**) {$[\alpha]_D^{20}$ +70 (*c* 0.6, MeOH)} with the reported values {lit.[3a] $[\alpha]_D$ −70 (*c* 0.9, MeOH) for (*S*)-**3**; lit.[7] $[\alpha]_D^{20}$ +74.6 (*c* 0.9, MeOH) for (*R*)-**3**} allowed us to confirm the absolute configuration of our synthetic isohaliclorensin (**3**) as *R*, which further confirmed the 2*R*,2′*R* stereochemistry assigned for 2-phenyl-2-(2-vinyl-piperidin-1-yl)-ethanol (**11a**) (vide supra).

Next, we turned our attention to the asymmetric synthesis of haliclorensin (**1**). Chemoselective reduction of the nitrile group of **4** (H_2, PtO_2, Norit, H_2SO_4, 96 h)[18] under acidic conditions provided the desired amido-amine **16** in 87% yield (Scheme 7). Treatment of **16** with 0.95 molar equiv of

Scheme 7



LHMDS in toluene at reflux led to the desired ring-expanded[19] product **17**[20] {mp 129−130 °C, $[\alpha]_D^{20}$ −5.6 (*c* 0.8, $CHCl_3$)} as a white solid in 43% yield (77% based on recovered starting material).

The final transformation of **17** to haliclorensin (**1**) turned out to be problematic. Attempts to reduce **17** with lithium aluminum hydride led to complex mixtures of products, with the desired product **1** only being isolated in low yield. Finally, it was found that the reduction of amide **17** with borane generated in situ from a $NaBH_4$−I_2 system[21] (THF, reflux, 16 h) provided the desired (*R*)-haliclorensin (*R*-**1**) {$[\alpha]_D^{20}$ 19.4 (*c* 0.8, MeOH); lit.[1] $[\alpha]_D$ −2.2 (*c* 1.3, MeOH) for natural **1**; lit.[3b] $[\alpha]_D$ −18.5 (*c* 0.6, MeOH) for (*S*)-**1**; lit.[3b] $[\alpha]_D^{20}$ 20 (*c* 2.0, MeOH) for (*R*)-**1**} in 75% yield.

Since the natural haliclorensin (**1**) was shown to consist of (*R*)- and (*S*)-enantiomers in a 1:3 ratio, with the (*S*)-enantiomer being predominant,[3b] we decided to pursue the synthesis of the (*S*)-enantiomers of haliclorensin (**1**) and isohaliclorensin **3**. Toward this end, Katritzky's method[12] was adopted for the synthesis of **11b**. Thus, treatment of **9** with 1.0 molar equiv of vinylmagnesium bromide at −78 °C, followed by reduction of crude **18** with $NaBH_4$ provided **11b** as the major diastereomer (dr = 89:11, overall yield, 54%)

(16) (a) Munchhof, M. J.; Meyers, A. I. *J. Org. Chem.* **1995**, *60*, 7084. (b) Andres, J. M.; Herraiz-Sierra, I.; Pedrosa, R.; Perez-Encabo, A. *Eur. J. Org. Chem.* **2000**, 1719. (c) For a related method, see: Guerrier, L.; Royer, J.; Grierson, D. S.; Husson, H.-P. *J. Am. Chem. Soc.* **1983**, *105*, 7754.

(17) Agami, C.; Couty, F.; Evano, G. *Tetrahedron Lett.* **1999**, *40*, 3709.

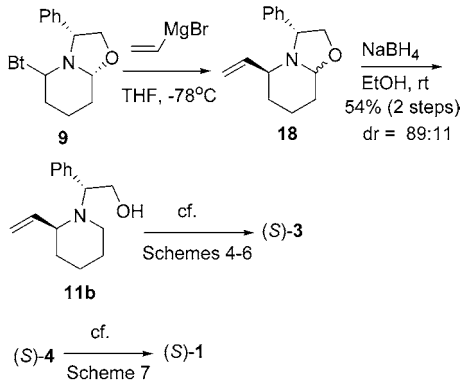
(18) Kramer, U.; Guggisberg, A.; Hesse, M.; Schmid, H. *Helv Chim. Acta* **1978**, *61*, 1342.

(19) For some other transamidation reactions, see: (a) Wasserman, H. H.; Berger, G. D.; Cho, K. R. *Tetrahedron Lett.* **1982**, *23*, 465. (b) Crombie, L.; Jones, R. C. F.; Osborne, S.; Mat-Zin, A. R. *J. Chem. Soc., Chem. Commun.* **1983**, 959. (c) Bienz, S.; Guggisberg, A.; Walchli, R.; Hesse, M. *Helv. Chim. Acta* **1979**, *62*, 1932. (d) Crombie, L.; Jones, R. C. F.; Haigh, D. *Tetrahedron Lett.* **1986**, *27*, 5147. (e) Crombie, L.; Jones, R. C. F.; Haigh, D. *Tetrahedron Lett.* **1986**, *27*, 5151. (f) Wasserman, H. H.; Robinson, R. P.; Matsuyama, H. *Tetrahedron Lett.* **1980**, *21*, 3493. (g) Manhas, M. S.; Amin, S. G.; Bose, A. K. *Heterocycles* **1976**, *5*, 669.

(20) Attempts to determine the enantiomeric excess of **17** by HPLC with several types of chiral columns were unsuccessful.

(21) Bhanu Prasad, A. S.; Bhaskar Kanth, J. V.; Periasamy, M. *Tetrahedron* **1992**, *48*, 4623.

Scheme 8



(Scheme 8). Compound **11b** was then converted to (*S*)-**3** and (*S*)-**1** using the procedures described for (*R*)-**3** and (*R*)-**1**, respectively (vide supra). In this way, (*S*)-isohaliclorensin (*S*-**3**) {$[\alpha]^{20}_D$ −69 (*c* 0.5, MeOH); lit.[3a] $[\alpha]_D$ −70 (*c* 0.9, MeOH) for (*S*)-**3**} and (*S*)-haliclorensin (*S*-**1**) {$[\alpha]^{20}_D$ −18.2 (*c* 0.4, MeOH); lit.[3b] $[\alpha]_D$ −18.5 (*c* 0.6, MeOH) for (*S*)-**1**} were obtained in overall yields comparable to those for (*R*)-**3** and (*R*)-**1**.

To summarize, starting from (3′*R*)-**9**, the first enantiodivergent syntheses of both enantiomers of isohaliclorensin (**3**) and haliclorensin (**1**) have been achieved. Notably, good agreement of the specific rotation values of both enantiomers of **1** and **3** with reported data implies that, under controlled conditions, racemization can be minimized during the ring expansion reactions.

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Supporting Information Available: Experimental procedures and spectral data for compounds **1**, **3**−**5**, **7**, **8**, **11**, **16**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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