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Asymmetric synthesis of isohaliclorensin, a key intermediate of bisquinolinylpyrrole alkaloid halitulin

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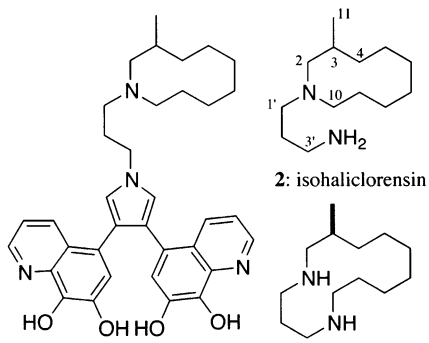
Abstract—A new enantioselective total synthesis of *N*-(3′-aminopropyl)-3-methylazacyclodecane, a partial structure of halitulin, has been achieved in eight steps with 14% overall yield. The key steps are the photochemical ring-expansion reaction of spirooxaziridine to lactam for constructing the azacyclodecane moiety and 1,4-stereoinductive methylation of the resulting lactam.

1. Introduction

A variety of structurally novel cytotoxic secondary metabolites, which are of interest as potential lead compounds for the development of new anti-cancer drugs, have been isolated from marine sponges.[1] Halitulin **1**, a novel bisquinolinylpyrrole, was isolated from the South African sponges *Haliclona tulearensis* by Kashman and co-workers, and found to be cytotoxic against several tumor cells such as P-388, A-549, HT-29 and MEL-28 in concentrations of 12–25 ng/mL.[2] The structure of **1** was elucidated by analysis of spectral data to have an *N*-(3′-aminopropyl)-3-methylazacyclodecane moiety **2** which is the proposed structure for haliclorensin, another unique alkaloid isolated from the same organism.[3] Being interested in the novel structures and biological activities of these compounds, several groups have achieved the total synthesis of **2**.[4] However, the proposed structure for haliclorensin has been the subject of much controversy. During the preparation of this manuscript, the structure of haliclorensin was revised to 7-methyl-1,5-diazacyclo-tetradecane **3**, and the synthetic isomer **2** was renamed isohaliclorensin.[5]5

Only a few methods are available for constructing macrocyclic amines.[6,7] The photochemical rearrangement reactions of oxaziridines afford lactams with high regioselectivity[8] and migration of the less substituted carbon occurs preferentially. This ring-expansion reaction has been applied to the synthesis of a number of



2: isohaliclorensin

1: halitulin **3**: haliclorensin

complex natural products and peptidomimetics. We have been very interested in utilizing this methodology to prepare medium-ring, nitrogen-containing compounds. Described herein is a new enantioselective total synthesis of **2** according to the following nitrogen insertion strategy (Scheme 1). The 10-membered chiral lactam thus obtained was 1,4-stereoselectively methylated to afford **6**.

2. Results and discussion

Our synthesis of isohaliclorensin commenced with the imine formation between commercially available cyclononanone and (*R*)-(−)-1-amino-1-phenyl-2-methoxyethane,[9] subsequent oxidation with *m*-CPBA gave spirooxaziridine **4** as a single diastereomer in 86% yield. Photolysis of **4** (254 nm, benzene, 6 h) followed by chromatographic separation afforded ring-expanded 10-membered lactam **5** in 57% yield.

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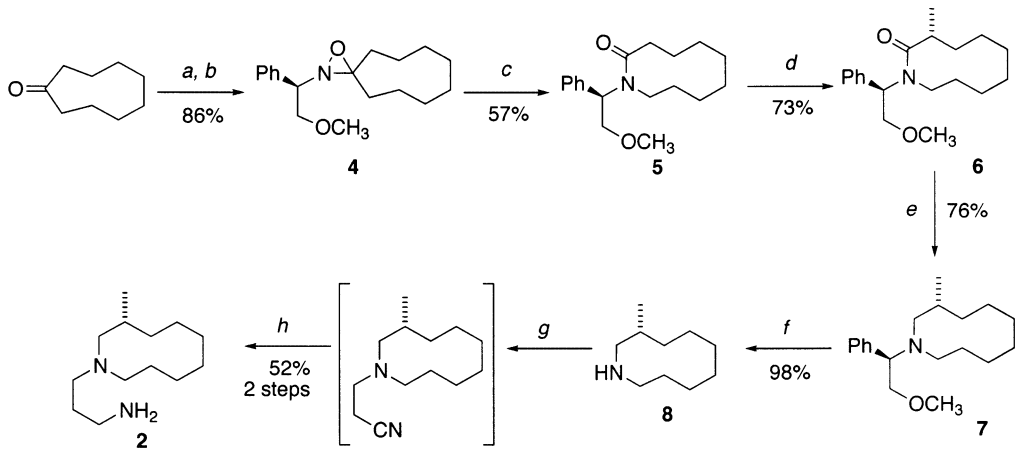

Scheme 1. *Reagents and conditions*: (a) (*R*)-(−)-1-amino-1-phenyl-2-methoxyethane (1.5 equiv.), toluene, reflux; (b) *m*-CPBA (1.5 equiv.), CH_2Cl_2, −78°C; (c) hν (254 nm), degassed benzene; (d) *sec*-BuLi (2.5 equiv.), CH_3I (3 equiv.), dry THF, −78°C; (e) $LiAlH_4$, dry THF, reflux; (f) $Pd(OH)_2$, 6 MPa H_2, aqueous MeOH, TFA, rt; (g) acrylonitrile (1.1 equiv.), dry MeOH, rt; (h) Raney-Ni, 3.5 MPa H_2, NH_3 saturated MeOH, rt.

1,4-Stereoinductive methylation of **5** was accomplished by treatment with *sec*-BuLi (2.5 equiv.) in THF at−78°C followed by addition of iodomethane to afford the product **6** as an inseparable 9:1 mixture of diastereomers in 73% yield. The ratio of diastereomers was determined from the ^1H NMR signals of the methyne protons adjacent to the nitrogen atom. Other chiral lactams corresponding to **5** were prepared from (*R*)-α-phenylethylamine or the MOM ether of (*R*)-2-phenylglycinol. The attempted increase in diastereoselectivity of the methylation using these lactams met with little success.

Reduction of **6** with $LiAlH_4$ in THF provided the desired macrocyclic amine **7** in 76% yield. Subsequent removal of the chiral auxiliary under hydrogenation conditions with $Pd(OH)_2$ in aqueous methanol in the presence of TFA produced 3-methylazacyclodecane **8** in quantitative yield.

Michael addition of amine **8** to acrylonitrile furnished β-aminonitrile, which was immediately hydrogenated over Raney-Ni in methanol saturated with NH_3 to afford **2** in 52% yield for two steps. Compound **2** thus prepared exhibits an $[\alpha]_D$ value of +74.6 (c= 0.925, MeOH), which is in good agreement with the $[\alpha]_D$ value of +71 (c=0.6, MeOH) observed for the (+)-(3*R*)-*N*-(3′-aminopropyl)-3-methylazacyclodecane.[4a] The stereochemistry of synthetic **2** was thus assigned as 3*R*.[10]

As summarized in Table 1, ^{13}C NMR spectral data of **2** correspond with those reported for the macrocyclic moiety of halitulin.[1] This suggests that the structure of halitulin has been correctly assigned. Synthetic studies for halitulin are now underway in our laboratories and will be reported in due course.

3. Experimental

3.1. General

All air and moisture sensitive reactions were carried out in flame-dried, argon-flushed, two necked flasks sealed with rubber septa, and the dry solvents and reagents were introduced with a syringe. Tetrahydrofuran (THF) was fleshly distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2) was fleshly distilled from phosphorus oxide. *m*-Chloroperbenzoic acid (*m*-CPBA) was washed with phosphate buffer (pH 7.4) and recrystallized from CH_2Cl_2. Benzene in the photochemical reaction was degassed by bubbling argon gas through it for 30 min under sonication. UV lamp was used on Sterilaire Lamp (254 nm, 90 W). Flash column chromatography was carried out on KANTO CHEMICAL silica gel 60 N (spherical, neutral, 40–50 μm), and pre-coated Merck silica gel plates (Art5715 Kiesel gel $60F_{254}$ 0.25 mm)

Table 1. ^{13}C NMR data for natural halitulin **1** and synthetic **2**

Carbon number	Natural halitulin δ_C (125 MHz, $CDCl_3$)	Synthetic **2** δ_C (100 MHz, $CDCl_3$)
2	57.7	60.8
3	28.3	30.0
4	32.7	32.0
5	24.4	22.2
6	24.2	26.6
7	23.9	24.7
8	23.6	24.3
9	22.0	26.0
10	50.9	53.3
11	20.7	19.5
1′	54.4	52.7
2′	26.1	31.1
3′	46.8	40.8

were used for TLC. Unless otherwise mentioned ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker DRX-600, JEOL JNM-LA400 or JEOL JNM-LA300 instruments. Coupling constants were determined directly from ^{1}H NMR spectra. Mass spectra (FAB) were obtained on JEOL JMS-700T or JEOL JMS-AX500 spectrometers. Optical rotations were measured on a JASCO P-1030 polarimeter with path length of 0.1 dm at ambient temperature; the concentrations are reported in g/dL.

3.2. (1′*R*)-2-(2′-Methoxy-1′-phenylethyl)-1-oxa-2-aza-spiro[2,8]undecane 4

In a round-bottomed flask equipped with a magnetic stirring bar and a Dean–Stark apparatus were placed cyclononanone (2.00 g, 14.3 mmol), (*R*)-(−)-1-amino-1-phenyl-2-methoxyethane (3.24 g, 24.2 mmol), *p*-toluenesulfonic acid monohydrate (80 mg) in toluene (80 mL), and the mixture was heated under reflux overnight. After cooling to room temperature, the resultant mixture was added to a solution of *m*-CPBA (3.76 g, 21.6 mmol) in CH_2Cl_2 (68 mL) at −78°C under an argon atmosphere, and stirred for 1.5 h. The reaction was quenched with 10% aqueous $Na_2S_2O_3$ (120 mL) and allowed to warm to room temperature. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), and dried over $MgSO_4$. Purification of the crude product by flash column chromatography (20% AcOEt in hexane) afforded **4** (3.56 g, 86%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43–7.26 (m, 5H), 3.86 (ddd, J=9.4, 5.8, 1.1 Hz, 1H), 3.71–3.69 (m, 1H), 3.66–3.64 (m, 1H), 3.35 (s, 3H), 1.89–1.78 (m, 3H), 1.72–1.42 (m, 13H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 138.0, 128.5, 127.8, 127.6, 85.8, 77.4, 66.4, 59.3, 37.1, 27.0, 26.5, 26.1, 25.8, 24.3, 23.5, 21.7. HRMS calcd for $C_{18}H_{27}NO_2$ 290.2120, found 290.2102 (M^+).

3.3. (1′*R*)-1-(2′-Methoxy-1′-phenylethyl)azacyclodecan-2-one 5

In a quartz schlenk flask equipped with rubber septum was placed a solution of oxaziridine **4** (1.52 g, 5.26 mmol) in degassed benzene (53 mL). Th e solution was irradiated with a UV lamp (254 nm) at room temperature for 6 h. The resultant mixture was concentrated. Purification of the crude product by flash column chromatography (30% AcOEt in hexane) afforded **5** (0.866 g, 57%). $[\alpha]_D$=−55.5 (c=1.25, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6, 80°C) δ 7.37–7.23 (m, 5H), 5.43 (t, J=6.6 Hz, 1H), 3.98–3.89 (m, 2H), 3.46–3.44 (m, 2H), 3.29 (s, 3H), 2.56–2.44 (m, 2H), 1.75–1.74 (m, 2H), 1.44–1.26 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 138.6, 128.4, 128.3, 127.6, 72.6, 58.7, 57.7, 44.3, 31.1, 27.8, 27.5, 26.2, 25.1, 21.8, 18.9. HRMS calcd for $C_{18}H_{27}NO_2$ 290.2120, found 290.2120 (M^+).

3.4. (1′*R*,3*R*)-1-(2′-Methoxy-1′-phenylethyl)-3-methyl-aza-cyclodecan-2-one 6

In a two-necked, round-bottomed flask equipped with an argon inlet, rubber septum and a magnetic stirring bar was placed a solution of lactam **5** (2.03 g, 7.03 mmol) in THF (60 mL). *sec*-BuLi (0.96 M solution in hexane, 18.3 mL, 17.6 mmol) was added at −78°C, and the mixture was stirred for 0.5 h. Then CH_3I (2.99 g, 21.1 mmol) was added at −78°C, and the mixture was stirred for 3 h. The reaction was quenched with saturated aqueous NH_4Cl (40 mL), and the mixture was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine (50 mL) and dried over Na_2SO_4. Purification of the crude product by flash column chromatography (10% AcOEt in hexane) afforded **6** (1.55 g, 73%). $[\alpha]_D$=−45.4 (c=0.625, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.27 (m, 5H), 5.88 (t, J=7.1 Hz, 1H), 4.00–3.90 (m, 2H), 3.66 (ddd, J=16.0, 12.7, 4.4 Hz, 1H), 3.41 (s, 3H), 3.28–3.23 (m, 1H), 2.93 (ddd, J=16.0, 5.8, 1.7 Hz, 1H), 2.02–1.95 (m, 1H), 1.69–1.25 (m, 9H), 1.11 (d, J=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 138.3, 128.5, 128.4, 127.5, 71.9, 58.7, 56.9, 42.8, 35.8, 34.8, 28.3, 28.2, 25.2, 22.1, 20.4, 18.8. HRMS calcd for $C_{19}H_{29}NO_2$ 304.2277, found 304.2296 (M^+); **minor isomer** (diagnostic peak only): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.23 (t, J=6.5 Hz, 1H), 3.37 (s, 3H), 1.08 (d, J=6.4 Hz, 1H).

3.5. (1′*R*,3*R*)-1-(2′-Methoxy-1′-phenylethyl)-3-methyl-azacyclodecane 7

In a two-necked, round-bottomed flask equipped with an argon inlet, rubber septum and a magnetic stirring bar was placed a suspension of the $LiAlH_4$ (0.402 g, 10.6 mmol) in THF (15 mL). A solution of lactam **6** (1.60 g, 5.29 mmol) in THF (10 mL) was added to the suspension at 0°C and the resulting mixture was heated under reflux overnight. After cooling to room temperature, excess $LiAlH_4$ was destroyed by cautious successive addition of water (6 mL), 10% NaOH (6 mL) and water (18 mL) with cooling in an ice bath. The mixture was filtered through a pad of Celite® and the filtrate was extracted with $CHCl_3$ (3×15 mL). The solid residue on Celite® was poured into THF (20 mL) and heated under reflux for 2 h. The resultant mixture was allowed to cool to room temperature and filtered through another pad of Celite®. The filtrate thus obtained and organic extracts were combined, and dried over $MgSO_4$. The crude product was purified by flash column chromatography (4% Et_2O in hexane) to afford **7** (1.16 g, 76%). $[\alpha]_D$=+43.8 (c=0.99, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.18 (m, 5H), 3.98–3.80 (m, 3H), 3.36 (s, 3H), 2.74–2.55 (m, 3H), 2.32–2.08 (m, 1H), 1.82–1.26 (m, 13H), 0.76 (d, J=6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 128.9, 128.7, 127.9, 126.7, 71.3, 62.7, 58.8, 56.9, 49.5, 31.5, 31.3, 26.6, 24.7, 23.7, 23.3, 19.6. HRMS calcd for $C_{19}H_{31}NO$ 290.2484, found 290.2483 (M^+); **minor isomer** (diagnostic peak only): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.33 (s, 3H).

3.6. (3*R*)-3-Methylazacyclodecane 8

In an autoclave was placed a solution of lactam **7** (0.587 g, 2.00 mmol) in MeOH (20 mL). Water (2 mL), TFA (0.15 mL, 2.00 mmol), and palladium hydroxide (20% on carbon, Pearlman's catalyst) (0.86 g) were added and hydrogenation was carried out at 6 MPa hydrogen pressure overnight. The resultant mixture was filtered through a pad of Celite®. The filtrate was

concentrated and partitioned between 3 M HCl (15 mL) and CH_2Cl_2 (15 mL). The aqueous layer was washed with CH_2Cl_2 (2×15 mL) and basified with NaOH pellets in small portions. The resulting mixture was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated (0.306 g, 98%). $[\alpha]_D = +17.4$ ($c = 0.205$, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85–2.72 (m, 3H), 2.44 (dd, $J = 12.6$, 9.3 Hz, 1H), 1.93–1.25 (m, 14H), 0.84 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.4, 48.4, 32.2, 31.4, 26.9, 26.0, 25.3, 24.4, 23.5, 20.2. HRMS calcd for $C_{10}H_{21}N$ 156.1752, found 156.1747 (M^+).

3.7. (3*R*)-1-(3′-Aminopropyl)-3-methylazacyclodecane 2

In a two-necked, round-bottomed flask equipped with an argon inlet, rubber septum and a magnetic stirring bar was placed a solution of amine **8** (0.155 g, 1.00 mmol) in MeOH (12 mL). At room temperature, acrylonitrile (0.0584 g, 1.10 mmol) was added to the solution, and the mixture was stirred overnight. The resultant mixture was concentrated and dissolved in MeOH (40 mL). The solution thus obtained was placed in an autoclave. Raney-Ni (catalytic amount) was added to the solution and hydrogenation was carried out at 3.5 MPa hydrogen pressure overnight. The resultant mixture was filtered through a pad of Celite®. The filtrate was concentrated and partitioned between water and $CHCl_3$ (15 mL). The aqueous layer was extracted with $CHCl_3$ (2×15 mL), and the combined organic layers were washed with water and 10% aqueous KOH (30 mL). The extraction was dried over Na_2SO_4 and concentrated to afford **2** (0.110 g, two steps 52%). $[\alpha]_D = +74.6$ ($c = 0.925$, MeOH); ^{1}H NMR (600 MHz, DMSO-d_6) δ 2.70 (ddd, $J = 13.1$, 10.6, 4.0 Hz, 1H), 2.59–2.47 (m, 3H), 2.33 (dd, $J = 12.5$, 11.9 Hz, 1H), 2.18 (ddd, $J = 13.0$, 4.5, 4.0 Hz, 1H), 2.12–2.08 (m, 2H), 1.91–1.73 (m, 3H), 1.68–1.62 (m, 1H), 1.59–1.29 (m, 11H), 1.52 (q, $J = 7.3$ Hz, 2H), 0.79 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 60.5 53.0, 52.6, 40.4, 31.8, 30.9, 29.6, 26.3, 25.6, 24.3, 24.1, 21.9, 19.5, (100 MHz, $CDCl_3$) δ 60.8, 53.3, 52.7, 40.8, 32.0, 31.1, 30.0, 26.6, 26.0, 24.7, 24.3, 22.2, 19.5. HRMS calcd for $C_{13}H_{28}N_2$ 213.2331, found 213.2334 (M^+).

Acknowledgements

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References

1. For examples, see: (a) Williams, D. E.; Lassota, P.; Anderson, R. J. *J. Org. Chem.* **1998**, *63*, 4838–4841; (b) Sakai, R.; Kohomoto, S.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *Tetrahedron Lett.* **1987**, *28*, 5493–5496.
2. Kashman, Y.; Koren-Goldshlager, G.; Gravalos, M. D. G.; Schleyer, M. *Tetrahedron Lett.* **1999**, *40*, 997–1000.
3. Koren-Goldshlager, G.; Kashman, Y.; Schleyer, M. *J. Nat. Prod.* **1998**, *61*, 282–284.
4. (a) Heinrich, M. R.; Steglich, W. *Tetrahedron Lett.* **2001**, *42*, 3287–3289; (b) Banwell, M. G.; Bray, A. M.; Edwards, A. J.; Wong, D. J. *New J. Chem.* **2001**, *25*, 1347–1350; (c) Hirakawa, H.; Goto, K.; Usuki, Y.; Iio, H. *Abstracts of Papers*, 43rd Symposium on the Chemistry of Natural Products, Osaka, October, 2001; Abstract 99 (P-56).
5. Heinrich, M. R.; Kashman, Y.; Spiteller, P.; Steglich, W. *Tetrahedron* **2001**, *57*, 9973–9978.
6. For a review of ring-closing olefin metathesis, see: Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450 and references cited therein.
7. Fujiwara, A.; Kan, T.; Fukuyama, T. *Synlett* **2000**, 1667–1669.
8. For a review, see: Aubé, J. *Chem. Soc. Rev.* **1997**, *26*, 269–277 and references cited therein.
9. Smith, A. B., III; Yager, K. M.; Taylor, C. M. *J. Am. Chem. Soc.* **1995**, *117*, 10882–10888.
10. Though the enantiomeric excess of **2** has not been rigorously determined, this apparent increase in enantiomeric purity may be the result of separation of diastereomers from their mixtures during the purification of **6** and **7**.