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Synthetic Approaches to Racemic Porantheridine and 8-Epihalosaline via a Nitroso Diels−Alder Cycloaddition/Ring-Rearrangement Metathesis Sequence

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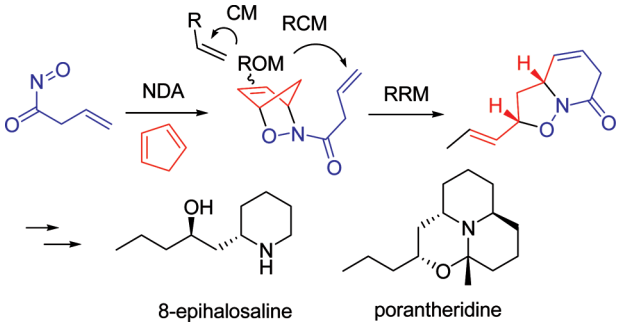
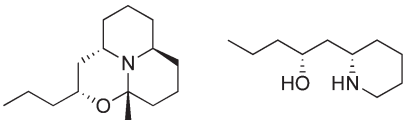


The application of a sequence involving a nitroso Diels−Alder cycloaddition and a ring-rearrangement metathesis to the total synthesis of (±)-8-epihalosaline and the formal synthesis of (±)-porantheridine is described. The formation of the 2,6-trans-disubstituted piperidine backbone of porantheridine has been accomplished by addition of a Grignard reagent onto an *N*-benzylpiperidone followed by a highly diastereoselective reduction of the imminium intermediate in one pot.

The abundance of biologically potent piperidines, indolizidines, and quinolizidines has resulted in intense synthetic efforts during the last decades.[1] Porantheridine (**1**) and 8-epihalosaline (**2**) are *syn*-2-(2-hydroxyalkyl)piperidine alkaloids (Figure 1). The tricyclic porantheridine (**1**)[2] was isolated from *Poranthera corymbosa* and 8-epihalosaline (**2**)[3] from *Andrachne aspera* Spreng.



1, porantheridine **2**, 8-epihalosaline

FIGURE 1. *syn*-2-(2-Hydroxyalkyl)piperidine alkaloids.

As part of the involvement of our group in the development of the nitroso Diels−Alder (NDA) reaction[4,5] we proposed the realization of the total syntheses of these alkaloids via the ring-rearrangement metathesis (RRM)[6] of NDA cycloadducts (Scheme 1).

It has been demonstrated by our research group that strained bicyclic *cis*-3,6-dihydro-1,2-oxazines with an alkene side chain obtained by NDA cycloaddition could be treated with Grubbs' II metathesis catalyst (**G-II**) in the presence of an external alkene to induce ring-opening metathesis (ROM), ring-closing metathesis (RCM), and cross-metathesis (CM) to yield isoxazolopyridinones **5**.[7] Such a structure (with R = Me, **5a**) could be seen as a precursor of 8-epihalosaline and porantheridine.

In practice, the synthesis of **5a** started with the conversion of but-3-enoic acid **6** to the corresponding hydroxamic acid **7**. Oxidation of the latter one with sodium periodate in presence of cyclopentadiene led to the desired nitroso Diels−Alder adduct **4** in 61% yield from **6**. The ring-rearrangement metathesis was then performed with 10 mol % of Grubbs' II catalyst (**G-II**) and an excess of but-2-ene gas affording the expected isoxazolopyridinone **5a** (75% yield). No significant amount of the isoxazolopyridinone that did not undergo cross-metathesis (R = H) was observed as is usually the case with terminal alkenes as cross-metathesis partners.[7]

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(2) Isolation: (a) Denne, W. A.; Johns, S. R.; Lamberton, J. A.; Mathieson, A. McL.; Suares, H. *Tetrahedron Lett.* **1972**, *13*, 1767–1769. (b) Johns, S. R.; Lamberton, J. A.; Sioumis, A. A.; Suares, H. *Aust. J. Chem.* **1974**, *27*, 2025–2034. Total syntheses: (c) Gossinger, E. *Tetrahedron Lett.* **1980**, *21*, 2229–2232. (d) Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* **1993**, *115*, 8851–8852. (e) David, M.; Dhimane, H.; Vanucci-Bacqué, C.; Lhommet, G. *J. Org. Chem.* **1999**, *64*, 8402–8405. (f) Takahata, H.; Ouchi, H.; Ichinose, M.; Nemoto, H. *Org. Lett.* **2002**, *4*, 3459–3462. (g) Takahata, H.; Saito, Y.; Ichinose, M. *Org. Biomol. Chem.* **2006**, *4*, 1587–1595. (h) Bates, R.; Lu, Y. *J. Org. Chem.* **2009**, *74*, 9460–9474.

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(4) Reviews on NDA: (a) Yamamoto, H.; Kawasaki, M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 595–607. (b) Yamamoto, Y.; Yamamoto, H. *Eur. J. Org. Chem.* **2006**, 2031–2043. (c) Yamamoto, H.; Momiyama, N. *Chem. Commun.* **2005**, 3514–3525. (d) Vogt, P. F.; Miller, M. J. *Tetrahedron* **1998**, *54*, 1317–1348. (e) Streith, J.; Defoin, A. *Synlett* **1996**, 189–200. (f) Kibayashi, C.; Aoyagi, S. *Synlett* **1995**, 873–879. (g) Streith, J.; Defoin, A. *Synthesis* **1994**, 1107–1117.

(5) (a) Galvani, G.; Calvet, G.; Blanchard, N.; Kouklovsky, C. *Org. Biomol. Chem.* **2008**, *6*, 1063–1070. (b) Calvet, G.; Guillot, R.; Blanchard, N.; Kouklovsky, C. *Org. Biomol. Chem.* **2005**, *3*, 4395–4401. (c) Calvet, G.; Dussaussois, M.; Blanchard, N.; Kouklovsky, C. *Org. Lett.* **2004**, *6*, 2449–2451.

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(7) Calvet, G.; Blanchard, N.; Kouklovsky, C. *Org. Lett.* **2007**, *9*, 1485–1488.

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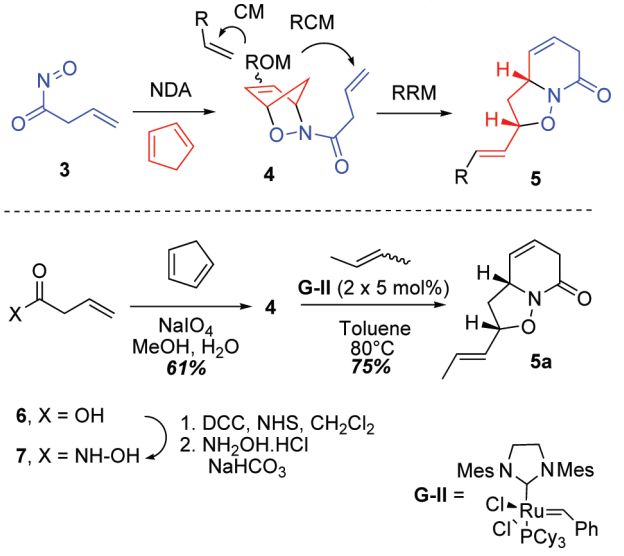
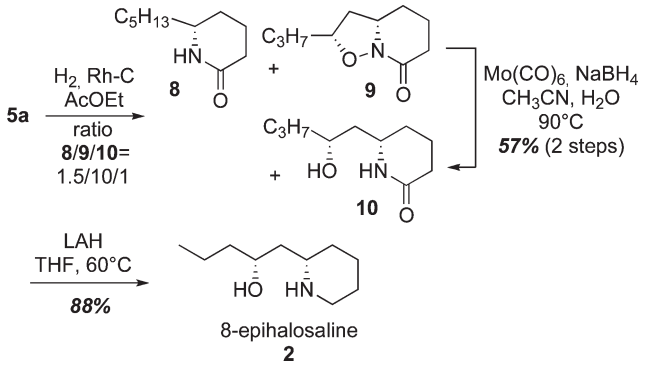
SCHEME 1. The Nitroso Diels−Alder (NDA) Cycloaddition/ Ring Rearrangement Metathesis (RRM) Sequence



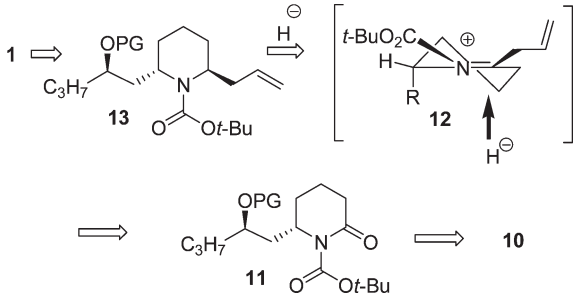
SCHEME 2. Total Synthesis of (±)-8-Epihalosaline



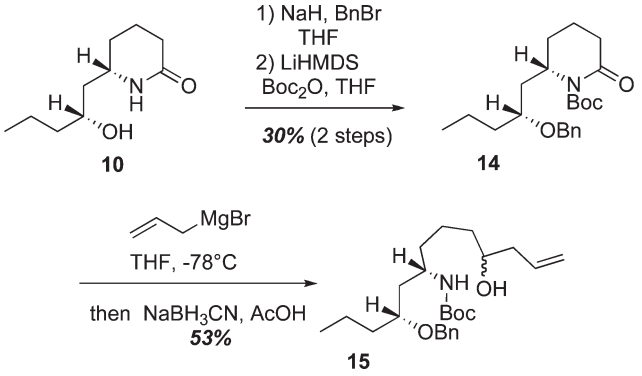
The synthesis of 8-epihalosaline is described in Scheme 2. Hydrogenation of the double bonds over Rh−C delivered **9** as the major product along with N−O cleavage product **10** and the deoxygenated compound **8** in a 10:1:1.5 (**9**/**10**/**8**) mixture.[8] Complete cleavage of the N−O bond was effected with subjection of the previous mixture with $Mo(CO)_6$ and $NaBH_4$[9] to yield **10** (57% over two steps). Finally, (±)-8-epihalosaline (**2**) was obtained by reduction of the amide with $LiAlH_4$ in 88% yield. All spectroscopic data of **2** were in agreement with the published data of 8-epihalosaline.[3]

The retrosynthetic analysis of porantheridine is described in Scheme 3. Addition of an allyl Grignard reagent to the *N*-Boc lactam **11** would lead to imminium species **12** of which the favored conformation has a pseudoaxial alkyl group at C2 to minimize steric interactions between the alkyl side chain at C2 and the nitrogen substituent.[10] The stereoelectronically preferred axial addition of an hydride should

SCHEME 3. Retrosynthesis of Porantheridine



SCHEME 4. Unsuccessful Formation of the 2,6-Trans-Disubstituted Piperidine 13



deliver the 2,6-trans-disubstituted piperidinic core **13** of porantheridine.[11]

In accord with the retrosynthetic scheme, the *O*-benzyl and *N*-Boc compound **14** was formed. Unfortunately, the addition of allylmagnesium bromide resulted in the opening of the *N*-Boc lactam and in the formation of alcohol **15** after hydride reduction instead of the expected piperidine **13** (Scheme 4).

We postulated that switching the *N*-Boc electron-withdrawing group to an *N*-alkyl group would prevent the opening of the lactam upon addition of the organometallic reagent. In fact, the stereoselective formation of 2,6-trans-disubstituted piperidines by direct addition of an organometallic reagent to *N*-alkylpiperidones followed by a hydride reducing agent has been overlooked since the pioneering work of Fowler with organolithium reagents,[12−15] although several groups have reported the synthesis of *cis*-substituted indolizidine or quinolizidine skeletons by a similar sequence on bicyclic lactams.[16] We decided to investigate this transformation with *N*-benzylpiperidone **16**.

Addition of allylmagnesium bromide onto dibenzylated compound **16** at room temperature followed by addition of sodium cyanoborohydride in acetic acid delivered stereoselectively the desired 2,6-trans-disubstituted piperidine **17** but

(8) The use of other hydrogenation catalysts resulted in the extensive formation of dehydrogenation compound **8**.

(9) Zhang, D.; Süling, C.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 885–888.

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(11) (a) Mill, S.; Hootelé., C. *Can. J. Chem.* **1996**, *74*, 2434–2443. (b) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289–296. (c) Deslonchamps, P. In *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; Chapter 6.

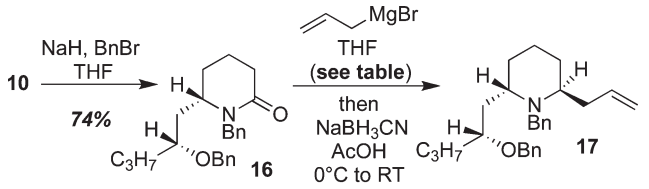
(12) (a) Hwang, Y. C.; Chu, M.; Fowler, F. W. *J. Org. Chem.* **1985**, *50*, 3885–3890. (b) Fréville, S.; Bonin, M.; Célérier, J.-P.; Husson, H.-P.; Lhommet, G.; Quirion, J.-C.; Thuy, V. M. *Tetrahedron* **1997**, *53*, 8447–8456.

(13) One related example of 2,3-cis-disubstituted piperidines from *N*-alkylpiperidones has been reported: Micouin, L.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1996**, *37*, 849–852.

(14) For related syntheses of 2,5-disubstituted pyrrolidines from *N*-alkylpyrrolidinones, see ref 12a and: Shibagaki, M.; Matsushita, H.; Kaneko, H. *Heterocycles* **1986**, *24*, 2315–2319.

(15) For the synthesis of 2,6-*trans*-disubstituted piperidines from thiolactams, see: Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919–1928.

SCHEME 5. Formation of the 2,6-Trans-Disubstituted *N*-Benzylpiperidine 17



Allyl Grignard	Temp.	Time	Yields **17**
3 eq.	rt	2 hr	*<10%*
7 eq.	reflux	3 hr	*17%*
7 eq.	50°C	3 hr	*51%*
3 eq.	45°C	30 min	*70%*

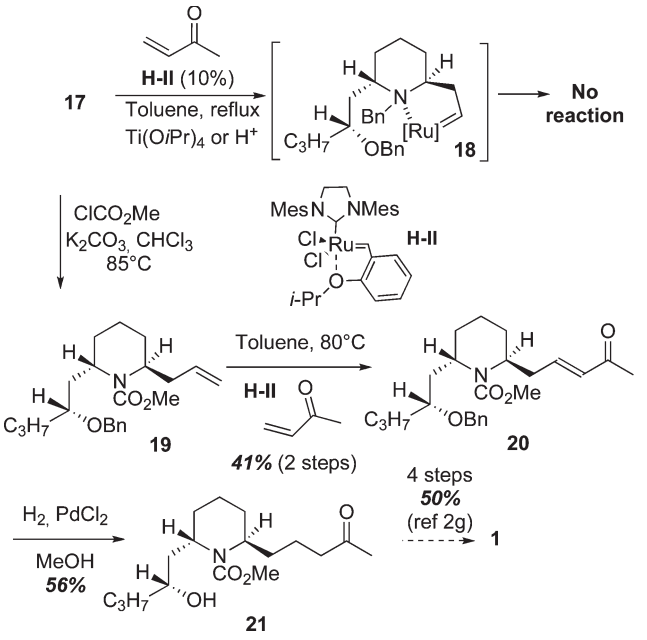
in low yield with recovery of the starting piperidone **16** (Scheme 5). Running the Grignard reaction in refluxing THF with a large excess of allylmagnesium bromide (7 equiv) during 3 h delivered **17** in 17% yields along with the product of double allyl addition. Lowering the temperature to 50 °C allowed us to obtain **17** in 51% yields. Eventually reducing the excess of the Grignard reagent to 3 equiv and the reaction time to 30 min resulted in a satisfactory 70% yield of **17** as a single diastereoisomer.[17] Presumably, the *N*-alkyliminium intermediate derived from **16** adopts the same conformation as the *N*-acyliminium intermediate **12**.

Cross-metathesis with methyl vinyl ketone was next required to complete the synthesis of porantheridine. Despite tremendous efforts, this operation was unproductive with *N*-benzylpiperidine **17**, most probably because of the coordination of the active ruthenium intermediate **18** by the lone pair of the nitrogen that prevents the reaction with the methyl vinyl ketone. Addition of Ti(O-*i*-Pr)$_4$ or Bronsted acids did not lead to any improvement.[18] To circumvent this problem, the *N*-benzyl group was replaced by a CO_2Me electron-withdrawing group.[19] To our satisfaction, the cross-metathesis compound **20** was thus obtained in 41% yields over two steps with Grubbs−Hoveyda II catalyst (**H-II**).

Hydrogenation of **20** with $PdCl_2$ allowed us to remove the *O*-benzyl protecting group and reduce the double bond of the enone and gave rise to compound **21**, which is an intermediate in the synthesis of porantheridine by Takahata.[2g] All spectroscopic data of compound **21** were in agreement with the published data. We have thus accomplished a formal synthesis of (±)-porantheridine (**1**) (Scheme 6).

In summary, the present work highlights the synthetic utility of a nitroso Diels−Alder cycloaddition/ring-rearrangement

SCHEME 6. Cross-Metathesis and Formal Synthesis of (±)-Porantheridine



metathesis sequence as demonstrated by the syntheses of the piperidinic alkaloids (±)-8-epihalosaline and (±)-porantheridine. In addition, the formation of the 2,6-trans-disubstituted piperidine framework of porantheridine features a rare Grignard addition onto an *N*-alkyl lactam followed by a highly diastereoselective reduction in one pot.

Experimental Section

2-(3-Butenoyl)-2-aza-3-oxabicyclo[2.2.1]-5-heptene (4). To a solution of *N*-hydroxysuccinimide (1.49 g, 12.95 mmol) in dichloromethane (15 mL) at 0 °C were added dicyclohexylcarbodiimide (2.55 g, 12.36 mmol) and but-3-enoic acid (1 mL, 11.77 mmol). The mixture was stirred for 2 h, and the insoluble dicyclohexylurea formed was removed by filtration. The filtrate was concentrated, and the crude hydroxamic acid was solubilized in diethyl ether and water. Hydroxylamine hydrochloride (2.03 g, 29.2 mmol) and sodium carbonate (2.1 g, 19.9 mmol) were successively added at 0 °C, and the mixture was stirred for 12 h. The heterogeneous mixture was then filtered with ethyl acetate. The filtrate was concentrated to yield the crude hydroxamic acid. Methanol and water were added to the crude hydroxamic acid, and then cyclopentadiene (5.07 mL, 61.5 mmol) and sodium periodate (3.73 mmol, 18.5 mmol) were successively added at 0 °C. The reaction was stirred for 30 min at 0 °C and 1.5 h at rt. The reaction was then quenched with an aqueous saturated solution of $NaHCO_3$ and extracted twice with ethyl acetate. The organic phase was dried with Na_2SO_4, filtered, and concentrated. The crude was purified by flash column chromatography (20% to 30% and 50% EtOAc/cyclohexane) to yield 1.24 g (61%) of the desired nitroso Diels−Alder cycloadduct **4**. ^{1}H NMR ($CDCl_3$): 6.50 (br s, 1H), 6.29 (d, J = 4.5 Hz, 1H); 5.87−5.77 (m, 1H); 5.27−5.03 (m, 4H); 3.05 (dd, J = 20.2, 8.5 Hz, 1H); 2.92 (br s, 1H); 1.92 (d, J = 10.4 Hz, 1H), 1.77 (d, J = 10.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): 174.9, 136.2, 132.4, 130.0, 118.0, 84.1, 61,8, 48.2, 39.7. IR (cm^{-1}): 3020, 1728, 1670, 1369, 1174, 924, 848, 802. HRMS (ESI): calcd 188.0682 ($C_9H_{11}NO_2Na$; $[M + Na]^+$), found 188.0697.

2-(1-Propenyl)isoxazolo[2,3-*a*]pyridin-7-one (5a). To the nitroso Diels−Alder cycloadduct **4** (840.0 mg, 5.09 mmol) in degassed toluene (100 mL) under argon at −78 °C was added the metathesis

(16) Selected examples: (a) Hwang, Y. C.; Fowler, F. W. *J. Org. Chem.* **1985**, *50*, 2719–2726. (b) Aubé, J.; Rafferty, P. S.; Milligan, G. L. *Heterocycles* **1993**, *35*, 1141–1147. (c) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398–404. (d) Comins, D. L.; Zheng, X.; Goehring, R. R. *Org. Lett.* **2002**, *4*, 1611–1613. (e) Gracias, V.; Zeng, Y.; Desai, P.; Aube, J. *Org. Lett.* **2003**, *5*, 4999–5001. (f) Yuguchi, M.; Tokuda, M.; Orito, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1031–1032. (g) Snider, B. B.; Grabowski, J. F. *J. Org. Chem.* **2007**, *72*, 1039–1042. (h) Ghosh, P.; Judd, W. R.; Ribelin, T.; Aubé, J. *Org. Lett.* **2009**, *11*, 4140–4142.

(17) The 2,6-trans-configuration was determined by the chemical shift of C_4 at 20.4 ppm, which is in agreement with typical values reported for 2,6-trans-disubstituted piperidine models. See ref 11a and: Eliel, E. L.; Kandasamy, D.; Yen, C.-y.; Hargrave, K. D. *J. Am. Chem. Soc.* **1980**, *102*, 3698–3707.

(18) Compain, P. *Adv. Synth. Catal.* **2007**, *349*, 1829–1846.

(19) (a) Barth, M. M.; Binet, J. L.; Thomas, D. M.; de Fornel, D. C.; Samreth, S.; Schuber, F. J.; Renaut, P. P. *J. Med. Chem.* **1996**, *39*, 2302–2312. (b) D'hooghe, M.; Dejaegher, Y.; De Kimpe, N. *Tetrahedron* **2008**, *64*, 4575–4584.

catalyst (216.0 mg, 0.254 mmol) **G-II**, and but-2-ene was bubbled in the reaction mixture at −78 °C for 2 min. The mixture was then heated to 80 °C for 3 h, 216.0 mg (0.254 mmol) of the metathesis catalyst was added, and the mixture was again heated to 80 °C for 3 h. After cooling, the reaction mixture was concentrated and then purified by silica gel flash column chromatography (5% MeOH/AcOEt), and 682.0 mg of isoxazolopyridone **5a** (75%) was isolated as a yellow oil. ^{1}H NMR ($CDCl_3$): 5.90−5.72 (m, 3H), 5.49 (dd, J = 15.0, 7.5 Hz, 1H), 4.74 (q, J = 8.2 Hz, 1H), 4.52−4.45 (m, 1H), 3.19 (ddt, J = 21.5, 5.0, 2.2 Hz, 1H); 2.98 (dt, J = 21.2, 3.6 Hz, 1H), 2.65 (dt, J = 11.8, 6.3 Hz, 1H), 1.80 (dd, J = 11.8, 9.0 Hz, 1H), 1.71 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$): 161.6, 131.6, 128.5, 123.0, 122.5, 81.6, 60.3, 40.9, 33.8, 17.7. IR (cm^{-1}): 2925, 1671, 1448, 1404, 1303, 966, 858, 737, 702. HRMS (ESI): calcd 202.0844 ($C_{10}H_{13}NO_2Na$; $[M + Na]^+$), found 202.0850.

8-Epihalosaline (2). A solution of **10** (78.9 mg, 0.426 mmol) in THF (4 mL) was added dropwise at 0 °C to a suspension of $LiAlH_4$ (48.3 mg, 1.28 mmol) in THF (3 mL). The reaction mixture was stirred at reflux for 3 h. The reaction was then cooled to 0 °C, 4 mL of water was added dropwise with caution, and 5 mL of AcOEt was also added. The white suspension was then filtered over Celite with AcOEt. The filtrate was concentrated and purified by silica gel flash chromatography (90% CH_2Cl_2, 8% MeOH, 2% NH_4OH) to yield 63.9 mg (88%) of 8-epihalosaline **2**. ^{1}H NMR ($CDCl_3$): 3.79−3.69 (m, 1H), 3.05 (br d, J = 13.3 Hz, 1H), 3.00 (br s, 1H), 2.74 (tt, J = 10.3, 2.5 Hz, 1H), 2.59 (dd, J = 13.3, 2.5 Hz, 1H), 1.85−1.77 (m, 1H), 1.68−1.03 (m, 12H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) 72.7, 58.3, 45.8, 42.3, 40.5, 33.9, 27.1, 24.4, 18.7, 14.2; IR (cm^{-1}) 3055, 2933, 1712, 1422, 1363, 1265, 739; HRMS (ESI) calcd 172.1701 ($C_{10}H_{22}NO$; $[M + H]^+$), found 172.1701.

(2*S,6*S**,2′*R**)-6-Allyl-1-benzyl-2-(2′-benzyloxypentyl)piperidine (17).** To 140.2 mg (0.377 mmol) of **16** in THF (4 mL) was added dropwise 1.13 mL of a 1 M solution of allylmagnesium bromide in THF, and the reaction mixture was heated to 45 °C for 30 min (no starting material was detected by TLC). The reaction was cooled to 0 °C, 120 mg (1.89 mmol) of $NaBH_3CN$ and 1 mL of AcOH were added, and the reaction was stirred for 2 h at 0 °C and 12 h at rt. The mixture was quenched with a saturated aqueous solution of $NaHCO_3$ and then solid $NaHCO_3$ until pH > 7. The aqueous phase was extracted twice with CH_2Cl_2, and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated. The crude was purified by flash chromatography (10% AcOEt/cyclohexane) to afford 104.4 mg (70%) of the desired 2,6-*trans*-piperidine **17**. ^{1}H NMR ($CDCl_3$): 7.45−7.18 (m, 10H), 5.78 (dddd, J = 17.2, 11.3, 7.1, 6.9 Hz, 1H), 5.00 (d, J = 17.2 Hz, 1H), 4.98 (d, J = 10.2 Hz, 1H), 4.40 (s, 2H), 3.77 (d, J = 13.9 Hz, 1H), 3.64 (d, J = 13.9 Hz, 1H), 3.48−3.32 (m, 1H), 2.95−2.77 (m, 2H), 2.43−2.27 (m, 1H), 2.24−2.21 (m, 1H), 2.07−1.96 (m, 1H), 1.60−1.10 (m, 11H), 0.85 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$): 141.3, 139.1, 137.1, 128.6, 128.5, 128.4, 128.2, 128.0, 127.8, 127.3, 126.5, 126.4, 126.2, 115.5, 76.5, 70.6, 54.2, 50.8, 49.8, 37.3, 36.0, 35.7, 26.9, 24.6, 20.4, 18.6, 14.2, IR (cm^{-1}): 2928, 1494, 1453, 1358, 1067, 910, 731, 697, HRMS (ESI): calcd 392.2948 ($C_{27}H_{38}NO$; $[M + H]^+$), found 392.2941.

(2*S,6*S**,2′*R**)-2-(2′-Benzyloxypentyl)-6-(4-oxo-2-pentenyl)-1-methoxycarbonylpiperidine (20).** To compound **17** (47.1 mg, 0.1203 mmol) in $CHCl_3$ were added K_2CO_3 (166 mg, 1.2 mmol) and methyl chloroformate (190 μL, 2.45 mmol). The mixture was stirred at 85 °C. Additional K_2CO_3 (85 mg, 0.61 mmol) and methyl chloroformate (95 μL, 1.22 mmol) were added after 48 and 60 h. After a total time of 72 h, the reaction mixture was filtered with CH_2Cl_2 and concentrated. The crude mixture was dissolved in toluene (2.4 mL), and then methyl vinyl ketone (60 μL, 0.736 mmol) and Hoveyda II catalyst **H-II** (11.3 mg, 0.018 mmol) were added. The reaction was stirred at 80 °C for 30 min under microwave irradiation. The reaction was charged again with Hoveyda II catalyst (11.3 mg, 0.018 mmol) and stirred again for 30 min under microwave irradiation at 80 °C. The crude mixture was then purified by flash chromatography (20−30% AcOEt/cyclohexane) to afford 19.8 mg (41%) of expected compound **20** as a yellow oil. ^{1}H NMR ($CDCl_3$): 7.35−7.26 (m, 5H), 6.74 (ddd, J = 15.4, 8.2, 6.4 Hz, 1H), 6.08 (d, J = 15.4 Hz, 1H), 4.56 (d, J = 11.6 Hz, 1H), 4.43 (d, J = 11.6 Hz, 1H), 4.09−4.02 (m, 1H), 3.95−3.87 (m, 1H), 3.67 (s, 3H), 3.47−3.39 (m, 1H), 2.75−2.65 (m, 1H), 2.44−2.35 (m, 1H), 2.28 (s, 3H), 2.04−1.93 (m, 1H), 1.78−1.29 (m, 11H), 0.92 (t, J = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): 198.5, 156.6, 145.2, 139.0, 132.9, 128.4, 128.2, 127.8, 127.5, 127.4, 76.4, 70.3, 52.3, 51.8, 49.4, 38.1, 37.5, 36.1, 27.0, 24.9, 24.8, 18.7, 15.0, 14.4. IR (cm^{-1}): 2929, 2870, 1694, 1674, 1445, 1362, 1253, 1098, 980, 735, 698. HRMS (ESI): calcd 424.2445 ($C_{24}H_{35}NO_4Na$; $[M + Na]^+$) found 424.2451.

(2*S,6*S**,2′*R**)-2-(2′-Hydroxypentyl)-6-(4-oxo-2-pentyl)-1-methoxycarbonylpiperidine (21).** To a solution of **20** (21.8 mg, 0.05436 mmol) in MeOH (1.5 mL) under argon was added 1.6 mg (0.009 mmol) of $PdCl_2$. Hydrogen was then bubbled in the reaction mixture for 10 min, and the reaction was stirred for 5 h under 1 atm of hydrogen. After being bubbled through argon for 10 min, the reaction mixture was filtered over Celite with AcOEt and concentrated. The crude mixture was then purified by flash chromatography (20−30% to 50% AcOEt/pentane) to afford 9.6 mg (56%) of expected compound **21** as a light yellow oil. ^{1}H NMR ($CDCl_3$): 3.96−3.92 (m, 1H), 3.79−3.73 (m, 1H), 3.69 (s, 3H), 3.62−3.54 (m, 1H), 2.47 (t, J = 5.5 Hz, 2H), 2.14 (s, 3H), 1.87−1.25 (m, 16H), 0.92 (t, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$): 208.8, 156.7, 69.7, 52.4, 51.9, 49.7, 43.6, 43.2, 40.1, 33.2, 29.9, 25.1, 23.9, 20.9, 18.8, 14.1, 13.9. IR (cm^{-1}): 3422, 2953, 2871, 1693, 1677, 1448, 1372, 1328, 1266, 1190, 1116. HRMS (ESI): calcd 336.2145 ($C_{17}H_{31}NO_4Na$; $[M + Na]^+$), found 336.2150.

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Supporting Information Available: Experimental procedures, characterization of compounds, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.