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Studies towards the total synthesis of halichlorine: asymmetric synthesis of the spiroquinolizidine subunit †

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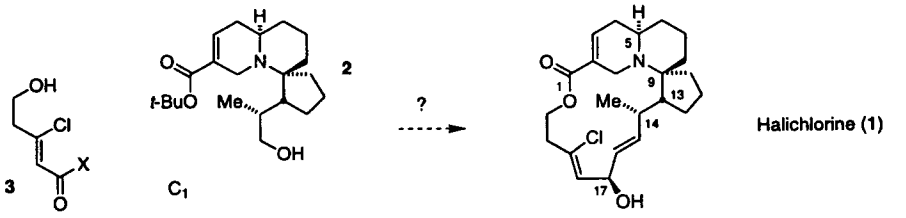
Abstract

The C1–C15 spiroquinolizidine subunit (cf. **2**) of the marine natural product halichlorine (**1**) was prepared in 12 steps starting from the known 'Meyers-lactam' **5**. The synthesis involves a *B*-alkyl-Suzuki coupling followed by a highly stereoselective intramolecular Michael addition and an intramolecular Mannich ring closure.

Halichlorine (**1**) is a novel marine alkaloid recently isolated from the sponge *Halichondria okadai* Kadota.[1] The compound has been claimed to selectively inhibit induced expression of VCAM-1 (Vascular Cell Adhesion Molecule-1) and might therefore be useful in the treatment of allergic inflammatory diseases and cancer.[2] This interesting biological profile, as well as the unusual architectural features of halichlorine, prompted us to initiate a research project aimed at its total synthesis.

Retrosynthetically, the molecule can be bisected into a spiroquinolizidine subunit (cf. **2**) and a fragment of the type **3**, containing the *Z*-vinylchloride moiety including two oxygen functionalities (Scheme 1). We now report a completely stereoselective, asymmetric synthesis of the spiroquinolizidine **2** which comprises 17 out of halichlorine's 23 carbons and features four of its five stereocenters.



Scheme 1.

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† We dedicate this paper to the accomplishments of Professor Albert Meyers.

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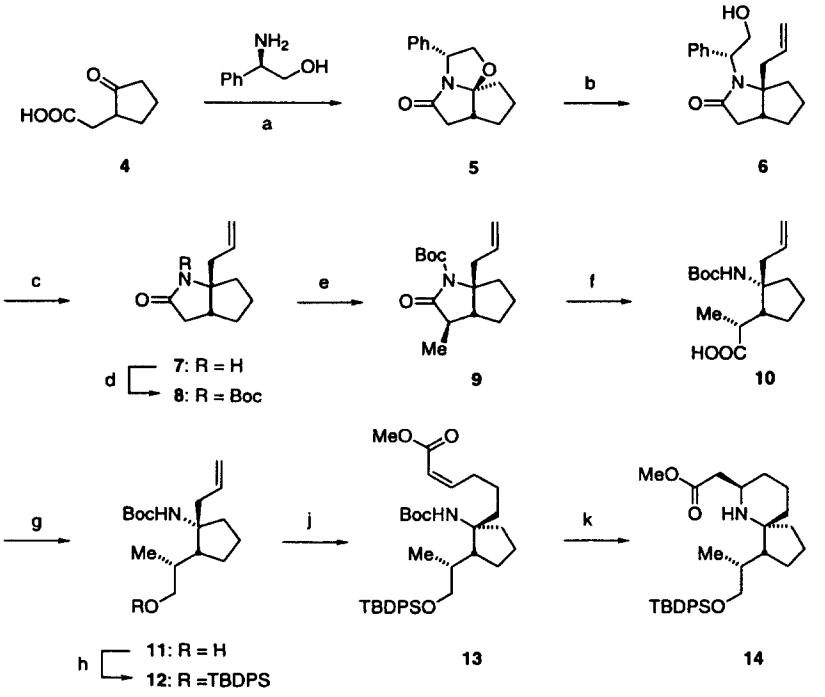
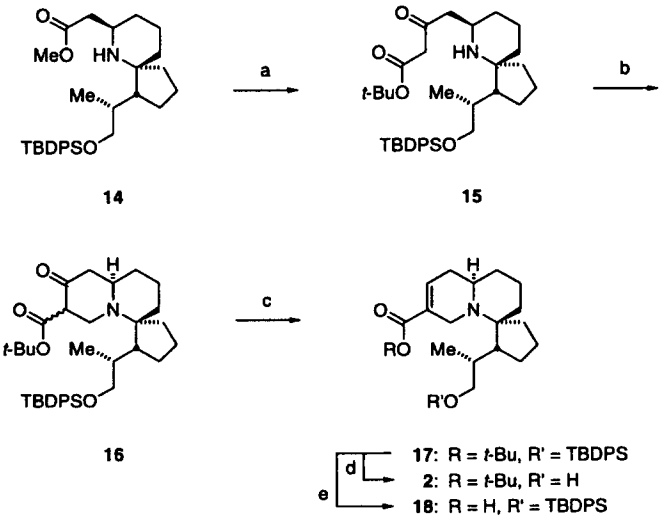
Our synthesis starts with the known 'Meyers-lactam' **5**[3] which was prepared from racemic carboxylic acid **4** and D-(−)-phenylglycinol as shown in Scheme 2. Treatment of **5** with excess allyltrimethylsilane in the presence of titanium tetrachloride furnished bicyclolactam **6** in virtually quantitative yield.[4] The efficiency of this reaction is probably due to the high reactivity of the strained bicyclic *N*-acyliminium ion intermediate.[5] Following reductive debenzylation (→**7**) and protection of the nitrogen atom, the resulting bicyclic *N*-Boc lactam **8** was stereoselectively methylated, as shown, to afford compound **9**. Unfortunately, all efforts to reduce **9** directly to the desired primary alcohol **11** failed. Accordingly, **9** was hydrolyzed to the interesting enantiomerically pure γ-amino acid **10** which was then activated as the mixed anhydride and reduced in situ with sodium borohydride.[6] The resulting primary alcohol **11** was protected as its *tert*-butyl-diphenylsilyl derivative **12**. Thus, three of the stereogenic centers had been installed in a fashion conductive to reaching halichlorine.



Scheme 2. Reagents and conditions: (a) PhMe, Δ (95%); (b) allyltrimethylsilane, $TiCl_4$, CH_2Cl_2, −78°C→rt (99%); (c) Na, NH_3, THF, EtOH, −78°C (92%); (d) Boc_2O, DMAP, THF (96%); (e) (i) LiHMDS, THF, −40°C; (ii) MeI, −78°C→0°C (90%); (f) LiOH, THF, H_2O (89%); (g) (i) ClCOOEt, Et_3N, THF; (ii) $NaBH_4$, MeOH (82%); (h) TBDPSCl, Et_3N, DMAP, CH_2Cl_2 (95%); (j) (i) 9-BBN, THF; (ii) *Z*-I–CH=CH–COOMe, Pd(dppf)Cl_2, $AsPh_3$, Cs_2CO_3, DMF, H_2O; (k) (i) TFA, CH_2Cl_2; (ii) H_2O, K_2CO_3 (77% overall from **12**)

The stage was now set for the construction of the heterocyclic ring system and the establishment of the stereocenter at C5. Our synthetic prospectus envisioned elongation of the allyl side chain followed by intramolecular addition of the nitrogen to a properly placed and suitably activated double bond. In the event, hydroboration followed by palladium mediated Suzuki-coupling,[7] with methyl *Z*-3-iodoacrylate, afforded the crude unsaturated ester **13** which upon deprotection of the amino function with TFA and subsequent basification underwent intramolecular Michael addition to afford piperidine **14** as the only isolated isomer in good overall yield.[8] The tight stereochemical control of this cyclization reaction can be rationalized in terms of a chair-shaped transition state wherein the larger substituents adopt pseudo-equatorial positions.

The transformation of the β-aminoster **14** into the fully functionalized spiroquinolizidine ring system **2** is shown in Scheme 3. Crossed Claisen condensation of **14** with *tert*-butyl acetate afforded β-keto ester **15** in good yield.[9] The quinolizidine ring system was closed by a Mannich reaction as shown. There was thus produced the β-keto ester, **16**, as a mixture of diastereomers and tautomers. Efficient conversion of the β-keto ester moiety to the corresponding α,β-unsaturated ester was achieved in one synthetic step and in excellent yield using Ganem's protocol.[10] The resulting dehydroquinolizidine, **17**, was deprotected with HF–pyridine to afford the primary alcohol **2**.[11] Alternatively, the *t*-Bu ester was cleaved under acidic conditions which after workup with aqueous bicarbonate solution, furnished free amino acid **18** in good yield.



Scheme 3. Reagents and conditions: (a) *t*-BuOAc, LiHMDS, THF, −50°C→rt (86%); (b) H_2CO, EtOH (73%); (c) (i) LiHMDS, THF, 0°C; (ii) $Cp_2Zr(H)Cl$, rt (91%); (d) HF–pyridine, THF (94%); (e) TFA, CH_2Cl_2, then $NaHCO_3$, H_2O (85%)

We note that compounds **2** (and **18**) potentially house a substantial segment of halichlorine. There remains the still formidable challenge of spanning the C1–C15 centers with the required intervening spacer domain. Programs to link compounds **2**, **18** or related constructs with suitably functionalized fragments corresponding to **3**,[12] as well as the application of our strategy to the synthesis of the closely related natural product pinnaic acid,[13] are being actively pursued.

Acknowledgements

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