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Synthesis of the substituted spiro segment of halichlorine—use of radical cyclization and stereospecific cuprate addition to an α,β-unsaturated lactam

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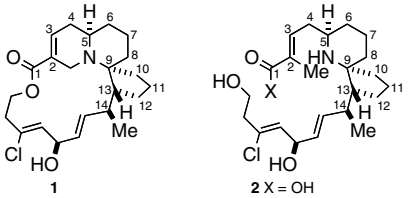
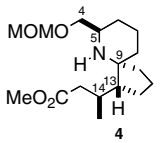
Abstract—Radical cyclization (**26a**,**b** → **27a**,**b**+**28**) and cuprate addition (**28** → **31**) were used as key steps to construct the spiro core **4** of halichlorine.

Halichlorine (**1**),[1,2] pinnaic acid (**2**),[3] and tauropinnaic acid (**3**)[3] are structurally related marine natural products with biological properties relevant to the study and treatment of inflammation. Both **1** and **2** have been synthesized by the Danishefsky school,[4,5] and a considerable body of work on the spiro core has been published.[6] We report the synthesis of compound **4** by a route based on radical cyclization and stereospecific cuprate addition to an α,β-unsaturated lactam as key steps. Compound **4** represents a substantial portion of the halichlorine structure, and appears to be suitably functionalized for explorations toward the natural product itself.





Our starting point is the readily available piperidine diester **6** (Scheme 1), which was made from pyridine 2,6-dicarboxylic acid by acid catalyzed esterification,[7] hydrogenation of the resulting hydrochloride salt over Pd–C,[7] and N-benzylation,[8] according to published procedures. The symmetrical diester **6** was then subjected to asymmetric allylation (**6** → **7**), using the bis-lithium salt of (1*S*,2*S*)-di[(*S*)-1-phenylethylamino]-1,2-diphenylethane[9] and allyl bromide.[10] Although **6** has been alkylated with other halides with very high ee,[10] in our hands, the allylation product had ee of only 69% and, for the purpose of the present work, we decided to accept that result. Reduction of both ester groups ($LiBH_4$, MeOH, 0–25 °C, 61%) gave diol **8**, and this was then treated with *t*-BuCOCl (*i*-Pr_2NEt, DMAP, CH_2Cl_2), in the expectation that the hydroxymethyl group at C(2) would be acylated. However, the main product (79% yield) was the equally useful regioisomer **9**, which was then protected as its methoxymethyl ether (**9** → **10**, $MeOCH_2Cl$, *i*-Pr_2NEt, DMAP, 95%). Hydroboration of the pendant double bond with 9-BBN gave alcohol **11** (94%), and the hydroxyl was then protected by silylation with *i*-$Pr_3SiOSO_2CF_3$ (**11** → **12**, 99%).

A number of compounds related to **12**, but having different protecting groups were also examined; however, only **12** proved suitable for further elaboration, and this was achieved as follows. Treatment with DIBAL-H served to remove the pivaloyl group (**12** → **13**, 96%), and Swern oxidation produced the expected aldehyde **14** (94%). This could be condensed with methyl propionate, giving **15a**,**b** as a separable mixture (ca. 2:3) of two isomers in a combined yield of 99%. Both isomers were

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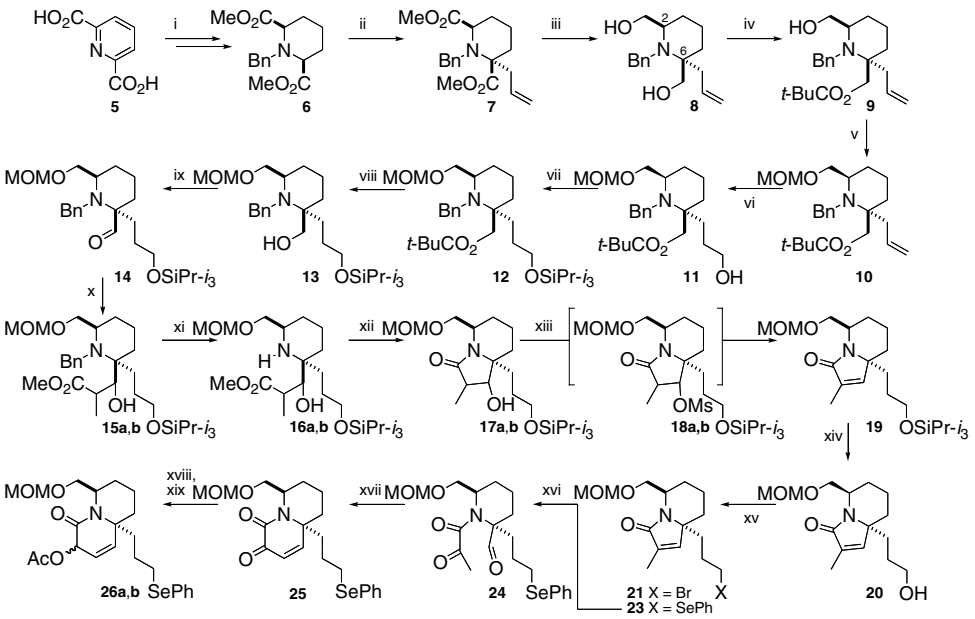
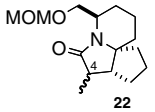


Scheme 1. Reagents and conditions: (i) as in Refs. 7,8; (ii) (1*S*,2*S*)-di[(*S*)-1-phenylethylamino]-1,2-diphenylethane, BuLi, THF, allyl bromide, 69%; (iii) $LiBH_4$, MeOH, 0 °C, then room temperature, 12 h, 61%; (iv) *t*-BuCOCl, *i*-Pr_2NEt, DMAP, CH_2Cl_2, −10 °C, 2 h, 79%; (v) $MeOCH_2Cl$, *i*-Pr_2NEt, DMAP, CH_2Cl_2, 0 °C, then 25 °C, 12 h, 95%; (vi) 9-BBN, THF, 0 °C, 15 min, then 25 °C, 12 h; 30% H_2O_2, MeOH, NaOH, 0 °C, then 25 °C, 2.5 h, 94%; (vii) *i*-$Pr_3SiOSO_2CF_3$, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 1 h, 99%; (viii) DIBAL-H, CH_2Cl_2–Et_2O, −78 °C, 20 min, 96%; (ix) Swern oxidation, 94%; (x) LDA, $MeO_2CCH_2CH_3$, THF, −78 °C, 1 h, then add **14**, 30 min, 58% (less polar isomer), 41% (more polar isomer); (xi) 10% Pd on charcoal, 1,4-cyclohexadiene, EtOAc, 58 °C, 30 min, 94% for less polar isomer, 95% for more polar isomer; (xii) PhMe, reflux, 48 h, 89% (less polar amine), 92% (more polar isomer); (xiii) MsCl, Et_3N, THF, 30 min, 0 °C, then 30 min, 25 °C, add DBU, reflux 12 h, 87% (less polar isomer), 90% (more polar isomer); (xiv) Bu_4NF, THF, 22 h, 94%; (xv) Ph_3P, 2,6-lutidine, CBr_4, CH_2Cl_2, 92% or PhSeCN, Bu_3P, THF, 98%; (xvi) O_3, CH_2Cl_2, −78 °C, then $(MeO)_3P$, −78 to 25 °C, 12 h, 81%; (xvii) DBU, THF, −10 °C, then 25 °C, 12 h, 64%; (xviii) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, −45 °C, 40 min, 85%; (xix) Ac_2O, pyridine, 12 h, 99%.

equally suitable for further use; they can be processed without separation, but in our initial experiments, we used the individual compounds. Brief heating (58 °C) with 10% Pd on charcoal in the presence of 1,4-cyclohexadiene allowed smooth removal of the *N*-benzyl group (ca. 95% in each case), and set the stage for the cyclization **16a**,**b** → **17a**,**b**. This was accomplished by prolonged refluxing (48 h) of a solution of the amines in PhMe. The resulting alcohols (**17a**,**b**) were mesylated in THF; DBU was then added to the reaction mixture, which was refluxed for 12 h. This procedure effected elimination via the intermediate mesylates **18a**,**b**, so that the two series of compounds afforded the same unsaturated lactam **19** (ca. 90% in both cases).

The siloxy group was now modified with a view to generating the five-membered ring of halichlorine by radical cyclization. To this end, compound **19** was first treated with Bu_4NF to release alcohol **20** (94%). The hydroxyl was initially replaced by bromine under standard conditions[11] (**20** → **21**, Ph_3P, 2,6-lutidine, CBr_4, 92%), but radical cyclization (Bu_3SnH, AIBN, slow addition, 80 °C, PhMe, 84%) gave an unsatisfactory stereochemical outcome, as the tricyclic lactams **22** were formed as a 1:4 mixture of compounds epimeric at C(4), with the undesired α isomer predominating. Equilibration by treatment with *t*-BuOK–*t*-BuOH almost reversed the ratio (3.3:1), but the compounds were difficult to separate, and we decided to modify our route in a way that inter alia afforded better stereochemical control. Alcohol **20** was converted into phenyl selenide **23** (PhSeCN,[12] Ph_3P, THF, 98%), and the double bond was then cleaved (**23** → **24**, 81%) by ozonolysis in CH_2Cl_2. The phenylseleno group survives[13] this transformation, provided the ozonide is reduced [$(MeO)_3P$] at a low temperature (−78 °C). The resulting keto aldehyde **24** was now subjected to intramolecular aldol condensation (**24** → **25**, 64%) by treatment with DBU. Application of this sequence to bromide **21** failed in the aldol step.



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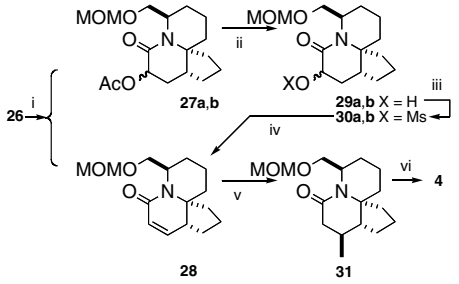
Attempted radical cyclization of **25** was unsuccessful, and we suspect that the enone substructure reacts in preference to the phenylseleno group. Accordingly, enone **25** was reduced ($NaBH_4$, $CeCl_3·7H_2O$, 85%), and acetylated (99%) to the mixture of acetoxy lactams **26a**,**b**. The individual acetates were now subjected to standard radical cyclization conditions (Scheme 2) and each gave a mixture of the derived tricyclic acetate (**27a**,**b**) and the unsaturated lactam **28**.

The less polar isomer of **26** gave **28** in 20% yield and the acetate in 67% yield. The more polar starting material gave corresponding products in 33% and 46% yield, respectively. The acetates **27a**,**b** were deacylated (**27a**,**b** → **29a**,**b**, MeONa, MeOH, ca. 90%) and the



Scheme 2. Reagents and conditions: (i) Bu_3SnH (addition over 10 h), AIBN, PhH, 80 °C, reflux 3 h more, less polar isomer of **26** gave **27a** in 20% yield, and **28** in 67% yield, more polar isomer of **26** gave **27b** in 33% yield and **28** in 46% yield; (ii) MeONa, MeOH, 4 h, 91% for less polar acetate, 92% for more polar acetate; (iii) $MeSO_2Cl$, Et_3N, THF; (iv) DBU, PhMe, reflux, 48 h, 69% over two steps for less polar alcohol; 64% for more polar alcohol; (v) Me_2CuLi, Me_3SiCl, Et_3N, THF, −78 °C, 2 h, then 25 °C for ca. 1 h, 81%; (vi) Me_3OBF_4, 2,6-di-*t*-butylpyridine, CH_2Cl_2, 4.5 h, aqueous Na_2CO_3, 71%.

resulting alcohols were mesylated in the usual way. The crude mesylates were treated with DBU in refluxing PhMe to produce **28** (69% for less polar alcohol, 64% for more polar alcohol). Introduction of the required methyl group in the correct stereochemical sense was now easily achieved by using Me_2CuLi in the presence of Me_3SiCl,[14] lactam **31** being produced in 81% yield. Initially, opening of the lactam proved very troublesome because semireduction with a variety of reagents was unsuccessful, but we eventually found that treatment of **31** with Meerwein's reagent,[15] followed by basic aqueous workup gave **4** in 71% yield.

Compound **4** represents the aza spiro system of halichlorine with the correct relative stereochemistry at each of the asymmetric centers, and the sidechain methyl group is in a configurationally stable location, since it is β to the ester carbonyl. The route to **4** illustrates two synthetically useful characteristics of a phenylseleno group: its ability to survive ozonolytic cleavage of a double bond,[13] and the fact that it serves as a radical trigger that is far less sensitive to basic conditions than bromine. At several points in this work steric or conformational factors led to unusual results; in particular we note the selective pivaloylation of the C(6) hydroxymethyl group of **8**, in preference to that at C(2). Lactam **31** has unusual properties: it is very easily reduced to the corresponding tertiary amine, and semireduction was not possible, even with LiH_2NBH_3, which is normally[6m,16,17] an effective reagent for this purpose. Our attempts to hydrolyze **31** (as well as lactam **22**) under standard basic or acidic conditions were unsuccessful, but the indirect procedure, via O-alkylation with Meerwein's reagent, worked well, and the resulting amino ester **4** showed little tendency to recyclize.

Acknowledgements

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