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Synthesis of a spirocyclic amine related to the marine natural products halichlorine and pinnaic acid

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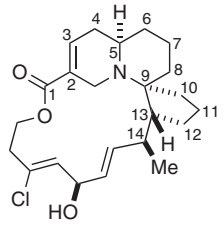
Abstract—The bis-ester **5** was elaborated into tricyclic lactam **8**, which has previously been converted into the spirotricyclic amine **9**, a compound that represents a large portion of the marine natural product halichlorine.

Halichlorine (**1**) and the pinnaic acids (**2**, **3**) have attracted considerable attention as synthetic targets—in part, because the substances have biological properties of interest to those studying various inflammatory processes. The Danishefsky school has reported the total syntheses of both **1**[1] and **2**[2] in optically pure form, while Christie and Heathcock[3] have completed syntheses of the same compounds as racemates. There is also a large literature[4] on synthetic studies that describe routes to the spirocyclic core of these compounds. In this regard, Huxford and Simpkins have recently reported[4g] a route from piperidine **4**, via allylated derivative **5**, to the spirocycle **6** (Scheme 1). Although the latter would require inversion of stereochemistry of the ester appendage at C-13 for elaboration into **1** or **2**, the synthesis illustrates the utility of the asymmetric allylation **4** → **5**, developed[6,7] a few years ago by the Simpkins group. We had previously used this asymmetric allylation in a synthesis of **7**[5] (Scheme 2) but had found that, in our hands,



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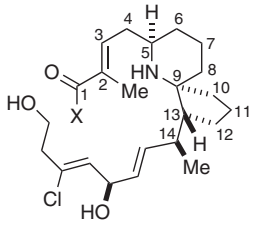
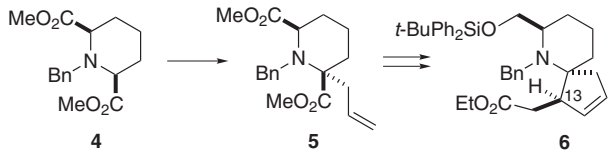
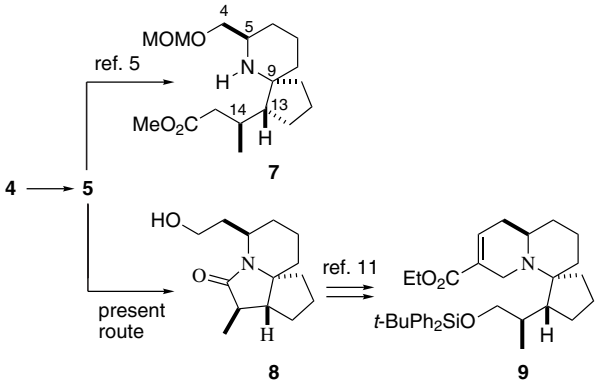


2 X = OH
3 X = $NHCH_2CH_2SO_3H$



Scheme 1.



Scheme 2.

the level of stereocontrol was poor, and the allylated compound **5** had an ee of only 67% (HPLC). As a result of correspondence with Professor Simpkins we have examined the allylation of both small (110 mg) and large (5–5.5 g) samples of **4** and found that the ee is sensitive to the scale of operation, and that the process gives poor results in large scale experiments.[8] Notwithstanding this outcome, we have continued to use the large scale allylation of **4**, and we describe here a synthetic route that is

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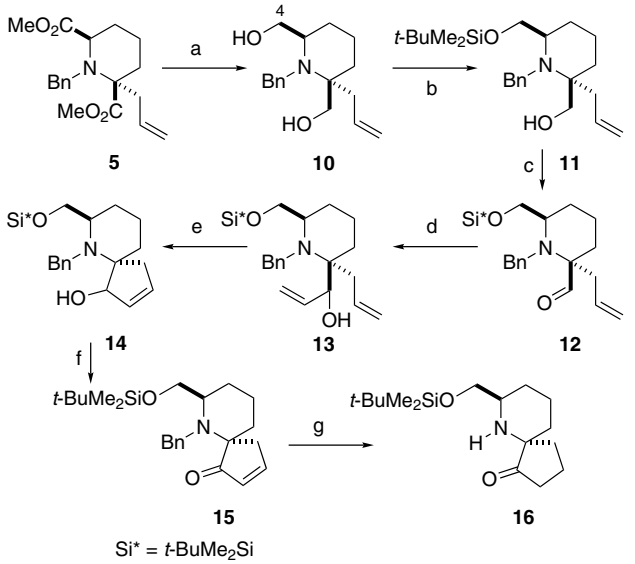
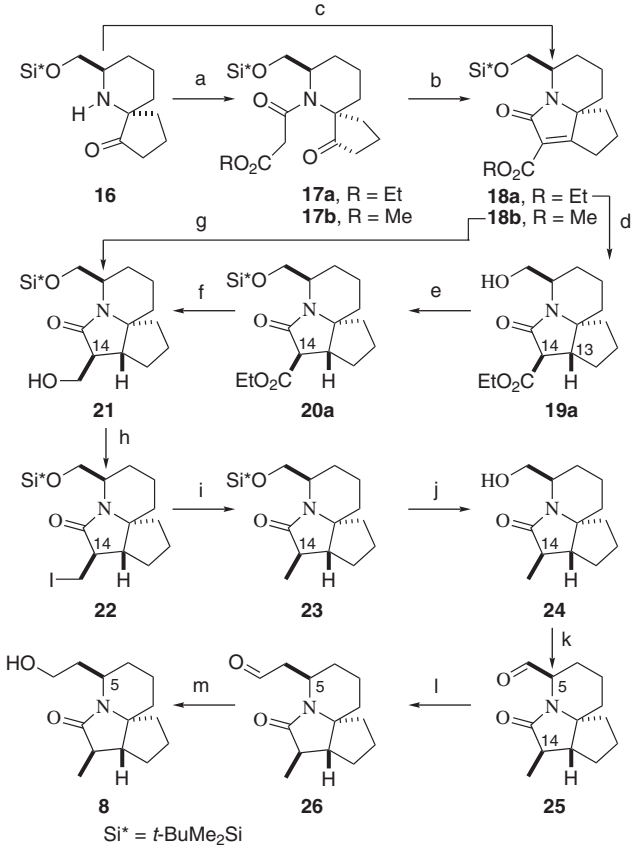
initially similar to the one just reported[4g] by Huxford and Simpkins, but which leads instead to the lactam **8** (Scheme 2). This tricyclic compound (in racemic form) has been converted[11] into the advanced intermediate (±)-**9**, whose relative stereochemistry is the same as in halichlorine; the corresponding optically active *tert*-butyl ester is an intermediate in the Danishefsky total synthesis.[1] Lactam (±)-**8** has also been elaborated[11] into the racemic version of an intermediate in the Danishefsky route[2] to pinnaic acid.

In the same way as described by Huxford and Simpkins, but using material of lower ee, the bis-ester **5** was reduced ($LiAlH_4$, 71%) and the less hindered primary hydroxyl in the product was protected (87%) as its *t*-BuMe_2Si ether (**5** → **10** → **11**). Interestingly, silylation occurs at the C-4 hydroxyl, whereas pivaloylation of the same alcohol resulted in the opposite regioselectivity.[5] Swern oxidation afforded aldehyde **12**, and reaction of the crude material with vinylmagnesium bromide gave the single alcohol **13** in 81% overall yield. (The whole process was much less efficient if an attempt was made to purify the aldehyde.) We did not establish the stereochemistry at the hydroxyl-bearing carbon, as that center is subsequently converted to sp^2 hybridization, but Huxford and Simpkins did make a stereochemical assignment (*S*) for the corresponding compound in which the C-4 alcohol is protected as a *t*-BuPh_2Si ether. Ring closing metathesis with 2 mol% Grubbs II catalyst in refluxing CH_2Cl_2 then gave the cyclopentenol **14** (85–95%), which was subjected to Swern oxidation (**14** → **15**, 72%). From this point our route differs from that of Huxford and Simpkins. The double bond in enone **15** was readily saturated by hydrogenation over Pd–C, with the *N*-benzyl group being removed at the same time (**15** → **16**, 86%) (Scheme 3).



Scheme 3. Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C, 5 h, 71%; (b) *t*-BuMe_2SiCl (0.80 equiv), imidazole, DMAP, CH_2Cl_2, 10 min, then *t*-BuMe_2SiCl (0.35 equiv), 30 min, 87%; (c) Swern oxidation, **12** is not very stable to flash chromatography over silica and is best used crude; (d) vinylmagnesium bromide, THF, −20 °C, 30 min, 81% from **11**; (e) 2 mol% Grubbs II catalyst, CH_2Cl_2, 35 °C, 4 h, 85–95%; (f) Swern oxidation, 72%; (g) Pd–C, EtOAc, H_2, 46 psi, 9.5 h, 86%.

The hindered nitrogen of **16** did not undergo acylation at all readily, but it did react with EtO_2CCH_2COCl in CH_2Cl_2 in the presence of Et_3N at 0 °C to afford **17a** (72%). Treatment with DBU in refluxing MeCN then effected both cyclization and dehydration to produce **18a**. The corresponding transformation in the methyl ester series (**16** → **17b** → **18b**) could be accomplished without isolation of any intermediates, and in better overall yield (83% vs 51%), by allowing **16** to react with MeO_2CCH_2-COCl at 0 °C in MeCN in the presence of Et_3N, followed by addition of DBU, and a 10 h reflux period. Compound **18a** was convertible into the advanced intermediate **21** by three simple steps. Catalytic hydrogenation of the double bond of **18a** gave **19a** (72%), in which epimerization had occurred at C-14, but the other newly-created stereocenter (C-13) was generated in the desired manner. Desilylation also took place during the reduction, and so this protecting group was reinstalled (**19a** → **20a**, 96%) under standard conditions.



Scheme 4. Reagents and conditions: (a) Et_3N, EtO_2CCH_2COCl, MeCN, 0 °C, then 4 h at room temperature; (b) DBU, reflux, 5 h, 51% from **16**; (c) Et_3N, MeO_2CCH_2COCl, MeCN, 0 °C, then removed ice bath, 4 h; DBU, reflux, 10 h, 83%; (d) Pd–C, EtOAc, H_2, 50 psi, 48 h, 72% ; (e) *t*-BuMe_2SiCl, imidazole, DMAP, CH_2Cl_2, 7 h, 96%; (f) DIBAL, PhMe, −78 °C, 15 min, then $NaBH_4$, MeOH, 5 h, 50%; (g) $LiBH_4$, THF–MeOH, 18 h, 87% ; (h) I_2, Ph_3P, imidazole, CH_2Cl_2, 3 h, 96%; (i) Bu_3SnH, AIBN, PhH, reflux, 4 h; (j) Bu_4NF, THF, 10 h, 99% from **22**; (k) Dess–Martin periodinane, CH_2Cl_2, 1 h, 93%; (l) $(Me_3Si)_2NK$, PhMe, $Ph_3PCH_2(OMe)Cl$, 0 °C, then 3 N HCl, aqueous THF, 3 h, ca. 75%; (m) $LiBH_4$, THF, 0 °C to room temperature (ice bath left in place but not recharged), 4 h, 87%.

Reduction of the ester group (DIBAL-H, followed by $NaBH_4$, 50%) then gave alcohol **21**. The same compound could be generated directly from enone **18b** by treatment with $LiBH_4$ (87%). We had initially intended to oxidize the resulting primary alcohol to the corresponding aldehyde, but our attempts to do so led only to the removal of the hydroxymethyl group and formation of a carbonyl at C-14. Accordingly, the hydroxyl was replaced by iodine (96%) using Ph_3P, I_2, and imidazole[12] (**21** → **22**), from which point stannane reduction gave the α-methyl lactam **23** (99%). Deprotection (Bu_4NF, THF, 99% overall from **22**) and oxidation with the Dess–Martin reagent afforded aldehyde **25** (93%), which was homologated (ca. 75% yield) to **26** by Wittig reaction with $Ph_3P{=}CH(OMe)$ (generated in PhMe with $(Me_3Si)_2NK$ as base), followed by mild acid hydrolysis (3 N HCl in aq THF, 3 h). The conditions for the Wittig reaction are critical, and use of a low (0 °C) temperature is essential. If the reaction is done at room temperature epimerization at C-5 occurs. Simple $LiBH_4$ reduction of crude aldehyde **26** gave alcohol **8** (87%); when the previous Wittig reaction was run at room temperature, the same sequence led to the C-5 epimer of **8**. Alcohol **8** has been converted into the spirotricyclic amine **9** (Scheme 4).[11]

The above experiments provide a new route to compounds relevant to the synthesis of halichlorine and the pinnaic acids. Our work also shows that proper temperature control must be exercised during homologation of aldehydes of type **25** by Wittig reaction, in order to suppress epimerization.

Acknowledgments

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8. Experimental details are given in Ref. 6 for asymmetric benzylation of **5**. By following that procedure (including the scale of operation) we obtained the benzylated product with $[\alpha]_D$ +32 (*c* 1.7, $CHCl_3$); the reported value (Ref. 6) is $[\alpha]_D$ +27 (*c* 1.7, $CHCl_3$). Our allylation experiments were modeled on the benzylation procedure; our chiral bis-amine had $[\alpha]_D^{25}$ +192 (*c* 0.97, $CHCl_3$); lit. (Ref. 7) +205 (*c* 0.7, $CHCl_3$). (a) With precooling of bis-ester solution: in a small scale allylation, the dilithium diamide was 0.0979 M, and the bis-ester solution [precooled to −78 °C (see Ref. 9 for description of the apparatus)], that was added over 5 min, was 0.0925 M (110 mg of bis-ester); neat allyl bromide (15 equiv, not precooled) was added over 2 min. The product (**5**) had $[\alpha]_D$ +40 (*c* 2.7, $CHCl_3$); the value observed by Simpkins et al. (private communication from Professor Simpkins) was $[\alpha]_D$ +33 (*c* 2.7, $CHCl_3$). In a large scale allylation, the dilithium diamide was 0.0818 M, and the bis-ester solution (precooled to −78 °C), that was added over 90 min, was 0.343 M (5.0 g of bis-ester); neat allyl bromide (3.3 equiv, not precooled) was added over 2 min. The product (**5**) had $[\alpha]_D$ +26 (*c* 2.7, $CHCl_3$). (b) Without precooling of bis-ester solution: in a second large scale allylation, the dilithium diamide was 0.0926 M, and the bis-ester solution, that was added over 90 min, but was not precooled, was 0.945 M (5.5 g of bis-ester); neat allyl bromide (3 equiv, not precooled) was added over 3 min. The product (**5**) had $[\alpha]_D$ +26 (*c* 2.7, $CHCl_3$). While we did not examine our sample of Simpkins' base used in the above experiments by HPLC, the $[\alpha]_D$ measurements we made on the allylation products show that there is significant erosion of ee in scaling up the allylation. (c) With precooling of bis-ester solution: two further experiments were performed, using concentrations close to those for our benzylation, but again, the ee (HPLC) for the large scale work was lower: the dilithium diamide was 0.11 M and the bis-ester solution (precooled to −78 °C), that was added over 10 min, was 0.09 M (110 mg of bis-ester); neat allyl bromide (15 equiv, not precooled) was added over 3 min. The product (**5**) had $[\alpha]_D$ +31.5 (*c* 1.0, $CHCl_3$) and had an ee of 66.5% (HPLC, Chiralcel OD, 25 cm × 0.46 cm, 1% *i*-PrOH–hexane, detection at 440 nm, flow1.2 mL/min). On a larger scale: the dilithium diamide was 0.09 M and the bis-ester solution (precooled to −78 °C), that was added over 2 h, was 0.10 M (5.0 g of bis-ester); neat allyl bromide (3 equiv, not precooled) was added over 5 min. The product (**5**) had $[\alpha]_D$ +24 (*c* 3.2, $CHCl_3$) and had an ee of 55.5% (HPLC). Cf. Ref. 10.
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