Total synthesis of dehaloperophoramidine using a highly diastereoselective Hosomi–Sakurai reaction

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The synthesis of dehaloperophoramidine, a non-halogenated derivative of the marine natural product perophoramidine, and its biological activity towards HCT116, HT29 and LoVo colorectal carcinoma cells is reported. A [3,3]-Claisen rearrangement and an epoxide opening/allylsilylation reaction installed the contiguous all-carbon quaternary stereocentres with the required relative stereochemistry.

The natural product (+)-perophoramidine (1) was isolated by Ireland from the marine ascidian Perophora namei.1 The authors also reported the structure of dehaloperophoramidine (2), which they obtained via transfer hydrogenation of (+)-1. These interesting alkaloids are structurally related to a more complex family of natural products that includes communesin F (3).2 Targets, including 1, 2 and 3, that possess contiguous all-carbon quaternary stereocentres present a significant synthetic challenge.3 The presence of this structural unit and the anticancer activity reported for 1 has led to several total and formal syntheses.4 Previous syntheses of 2 have involved a spirocyclisation of a 2-thiotryptamine analogue,5 a dearomatising arylation of a quinoline6 and an efficient synthesis from a commercially available indigo dye.7

In work aimed at the synthesis of the communesins, we have explored a [3,3]-Claisen approach to establish the required C7 stereocentre in 3 (Fig. 1).8 In the first part of this new report we describe a significant extension of this work resulting in the large scale synthesis (62 grams) and resolution of a novel ketone using our [3,3]-Claisen rearrangement method (Scheme 1). This highly efficient sequence, that does not require chromatographic purification in any of the first five steps, enables access to enantio-enriched ketones. Whilst we view these ketones as flexible starting points for the synthesis of a number of optically pure complex ring systems, here we report conversion of racemic material to 2.

Our retrosynthetic analysis of 2 (Scheme 1) identified lactam 4 as the cornerstone of the approach. Lactam 4 was viewed as accessible from diallyl-substituted alcohol 5, which contains both the required C-10b and C-11 stereocentres. A key challenge in this part of the synthesis was the need to differentiate between the two allyl groups in 5. This was achieved using two different selective iodocyclisation protocols. Whilst this transformation is preceded in simpler systems,9 it has been used sparingly in the synthesis of more complex alkaloid-based structures.10
Alcohol 5 could be prepared from allyl-ketone 6, which itself could be constructed from commercially available 7 and 8.

The key challenge in the conversion of 6 to 5 is the incorporation of the second contiguous all carbon stereogenic centre with the required relative stereochemistry. Conversion of the ketone in 6 to the corresponding epoxide was planned. Subsequent Lewis acid catalysed epoxide opening followed by trapping with allylsilane was predicted to lead to 5 with the approach of the allyl nucleophile occurring from the opposite face to the allyl group that is already present. This reaction, which we refer to as a modified Hosomi–Sakurai reaction,11 has been used in natural product synthesis,12 but to the best of our knowledge has not been used in the construction of contiguous all-carbon quaternary centres. Alternative approaches to lactam 4 involving the early development of the allyl group in 6 or alkylation of a C11-based ester were explored but were either ultimately unsuccessful or led to significantly longer reaction sequences (data not shown).

The C10b stereocentre in 6 was installed in 5 steps from 7 and 8 as described in Scheme 2. After coupling of 7 and 8 to give 9, the tetracyclic system was formed using a high temperature electro-philic aromatic substitution reaction (see Scheme S1 (ESI)† for additional studies). The cyclisation was scalable up to 100 g with no detrimental effect on the yield. Functional group manipulations then enabled the preparation, via 10, of the [3,3]-Claisen rearrangement substrate 11. Highly efficient conversion of 11 to the required novel ketone 6 occurred on heating in toluene for 1.5 hours in 88% yield. This reaction was robust and scalable with 62 g of 6 being prepared in a single batch and without the need for purification by column chromatography at any stage. Ketone 6 could be resolved by treatment with (R)-tert-butanesulfanilamide (12) to generate the readily separable diastereomeric imines 13 and 14 (Scheme 3). This approach was inspired by the reported resolution of a ketone-containing intermediate en route to epiboxidine.14 Hydrolysis of imines 13 and 14 with 12 M HCl in MeOH gave (R)-6 and (S)-6 respectively in >99% ee after recrystallisation (confirmed by chiral HPLC analysis†). The absolute configuration of the intermediate imines 13 and 14 were assigned following X-ray crystallographic analysis of 1515 which was obtained following diastereoselective reduction of 14 with NaBH₄ (Scheme 3). The X-ray analysis indicated that the absolute configuration of the C10b stereogenic centre in 15 (and hence in 14) was (R).

Hydrolysis of imine 14 therefore provided the (S)-enantiomer of 6 (and 13 gave (R)-6). Whilst (R)-6 and (S)-6 have been prepared, their conversion to enantio-enriched alternative complex ring systems will be reported in the future. Here we decided to continue the development of a route to 2 using the much larger quantities of (±)-6 available to us.

With the novel ketone 6 in hand, the ketone functionality was converted to the corresponding epoxide using CICH₂I16 (see Scheme S2 (ESI)†) for the stereochemical assignment of 16.13 Allylsilylation of 16 under Lewis acidic conditions with allylTMS (17) in a modified Hosomi–Sakurai reaction11 gave the desired alcohol 5 as a single diastereoisomer (as judged by ¹H NMR analysis of the crude reaction mixture). This reaction proved highly robust and scalable with ca. 42 g of 16 being reproducibly converted to 38 g of 5. X-ray crystallographic analysis of 5 confirmed the required anti-relationship of the two allyl substituents at C-10b and C-11 (Scheme 4 and Scheme S3, ESI)†.13

The challenge of selectively functionalising the two allyl groups in 5 now had to be overcome. A two-step oxidation of 5, followed by regioselective iodolactonisation gave 18 and its epimer at the indicated carbon as an inconsequential mixture of diastereoisomers (Scheme 5, d.r. 3:1). The relative configuration of the newly formed stereocentre in the major isomer 18 was determined by NOE analysis (Scheme S4 and Fig. S2–S4, ESI)†.13 Oxidative cleavage on treatment with catalytic OsO₄ and NMO followed by in situ reaction with Phl(OAc)₂ gave 19 and its epimer (Scheme 5 and Scheme S5, ESI)†.13 After incorporation of the required nitrogen by reductive amination using (±)-1,27 (Scheme 3), retro-iodolactonisation to give the diastereomeric mixture 20, acid-mediated deprotection and subsequent treatment of 21 with HBTU and DIPEA, lactam 4 was obtained. However, cyclisation
iodoethylation to give 22 (and its epimer, d.r. 11:1, Fig. S6, ESI†) in the presence of iodine under basic conditions. A one-pot oxidative cleavage of the alkene gave 23 (and its epimer) which underwent successful reductive amination with (R)-12 followed by a retro-iodoethylation in the presence of Zn to generate the diastereomeric mixture 24. Oxidation of 24 with the Dess–Martin periodinane18 gave 25 in a reasonable yield (52%) for this relatively complex process which also involves acid-mediated deprotection of the sulfinate. Interestingly, 25 underwent oxidation with NaClO₂ to give the required lactam 4. This transformation was inspired by a report by Tomioka et al. on an unrelated system.†

The new approach was robust and overall reduced the length of the reaction sequence to 4.

Having successfully synthesised the desired lactam 4, its conversion to 2 was completed (Scheme 6). The remaining alkene in lactam 4 was oxidatively cleaved and the resulting aldehyde reductively aminated using MeNH₂-HCl under basic conditions to give 26 (Scheme 6). Boc protection of 26 gave 27 which underwent alkylation with Meerwein’s reagent20 to give 28. Deprotection of 28 with trifluoroacetic acid gave 29 which cyclised on refluxing in toluene to give N-benzyl-dehaloperoxomorphamide (30) in excellent yield. X-ray crystallographic analysis of 30 confirmed the successful formation of the C-4’ amidine motif.15 The synthesis of 2 was completed by N-benzyl deprotection of 30 via a single electron transfer process with a freshly prepared solution of sodium naphthalenide.21

Synthetic 2 was converted to the corresponding TFA salt13 and compared to an authentic sample of 2-TFA (Fig. S7–S9, ESI†). A doping experiment with authentic 2-TFA and synthetic 2-TFA confirmed that the desired compound had been successfully prepared (see Fig. S8A and B, ESI† for a comparison of a selected region of the 1H NMR analysis carried out in CD₂OD). Superimposition of the 1H NMR of the doped sample with the of 20 to 4 proved irreproducible (for further discussion see Schemes S6–S8 and Fig. S5, ESI†). An alternative route to 4 was investigated in an attempt to circumvent the reproducibility issue. Di-allyl alcohol 5 underwent a regio- and highly diastereo-selective

Scheme 4 Construction of all-carbon quaternary stereocentres. The ORTEP representation of 5 is also shown.15

Reagents and conditions: (a) ClCH₂I (1.1 eq.), MeLiBr (2.2 M solution in Et₂O, 1.5 eq.), THF, rt, 16 h, 72%; (b) allylTMS (2.5 eq.), Ti(OEt)₄ (4 eq.), CHCl₃, rt, 16 h, then NaBH₄ (4 eq. in MeOH), 0.5 h, rt, 75%; (c) NIS (1.1 eq.), NaHCO₃ (1.1 eq.), DCM, rt, 16 h, d.r. 3:1, 47% (over 5 steps from 7); (d) OsO₄ (0.13 mol%), NMO (1.5 eq.), acetone/H₂O (10:1), rt, 18 h, then PhI(OAc)₂ (1.5 eq.), rt, 1.5 h, 86%; (e) (±)-12 (1.1 eq.), TiOEt₄ (3 eq.), CHCl₃, rt, 16 h, then NaBH₄ (4 eq. in MeOH), 0.5 h, rt, 75%; (f) Zn, ETOH, reflux, 16 h, 89%; (g) 4 M HCl in dioxane/MeOH (10:1), rt, 1 h, then HBTU (1.5 eq.) and DIPEA (2 eq.), toluene, reflux, 16 h, 83% (over 2 steps); (h) PhI(OAc)₂ (1.5 eq.), rt, 1.5 h, 86%; (i) OsO₄ (3.2 mol%), NMO (1.5 eq.), THF/H₂O (10:1), rt, 16 h, then PhI(OAc)₂ (1.5 eq.), rt, 1.5 h, 86%; (j) (±)-12 (1.1 eq.), TiOEt₄ (2 eq.), CHCl₃, rt, 16 h, then NaBH₄ (5 eq.) in MeOH, rt, 1 h, 68%; (k) Zn (31 eq.), EtOH, reflux, 16 h, 80%; (l) Dess–Martin periodinane (1.5 eq.), DCM, rt, 0.5 h, 52%; (m) NaClO₂ (2.5 eq.), NaH₂PO₄ (5 eq.), 2-methylbuten-2-ene (10 eq.), THF/H₂O (1.5:1), rt, 2 h, 58%.

Scheme 5 Two alternative approaches to lactam 4. Reagents and conditions: (a) PCC (1.1 eq.) DCM, rt, 16 h; (b) Jones reagent (1.5 eq.), acetone, rt, 16 h; (c) NIS (1.1 eq.), NaHCO₃ (1.1 eq.), DCM, rt, 16 h, d.r. 3:1, 47%, (over 5 steps from 7); (d) OsO₄ (0.13 mol%), NMO (1.5 eq.), acetone/H₂O (10:1), rt, 18 h, then PhI(OAc)₂ (1.5 eq.), rt, 1.5 h, 86%; (e) (±)-12 (1.1 eq.), TiOEt₄ (3 eq.), CHCl₃, rt, 16 h, then NaBH₄ (4 eq. in MeOH), 0.5 h, rt, 75%; (f) Zn, ETOH, reflux, 16 h, 89%; (g) 4 M HCl in dioxane/MeOH (10:1), rt, 1 h, then HBTU (1.5 eq.) and DIPEA (2 eq.), toluene, reflux, 16 h, 83% (over 2 steps); (h) PhI(OAc)₂ (1.5 eq.), rt, 1.5 h, 86%; (i) OsO₄ (3.2 mol%), NMO (1.5 eq.), THF/H₂O (10:1), rt, 16 h, then PhI(OAc)₂ (1.5 eq.), rt, 1.5 h, 86%; (j) (±)-12 (1.1 eq.), TiOEt₄ (2 eq.), CHCl₃, rt, 16 h, then NaBH₄ (5 eq.) in MeOH, rt, 1 h, 68%; (k) Zn (31 eq.), EtOH, reflux, 16 h, 80%; (l) Dess–Martin periodinane (1.5 eq.), DCM, rt, 0.5 h, 52%; (m) NaClO₂ (2.5 eq.), NaH₂PO₄ (5 eq.), 2-methylbuten-2-ene (10 eq.), THF/H₂O (1.5:1), rt, 2 h, 58%.

Scheme 6 Completion of the synthesis of (±)-2. Reagents and conditions: (a) OsO₄ (3.2 mol%), NMO (1.5 eq.), THF/H₂O, rt, 16 h, then PhI(OAc)₂ (1.5 eq.), rt, 1 h, 62% (over 2 steps from 25); (b) MeNH₂-HCl (2.5 eq.), NaOAc (2.5 eq.), MeOH, rt, 16 h, then NaBH₄ (3 eq.) in DCM, 0 °C – rt, 2 h, 72%; (c) Boc₂O (1.5 eq.), TEA (1.5 eq.), rt, 1 h, 44% (2 steps); (d) Meerwein’s reagent (1 M solution in DCM, 8 eq.), DIPEA (8 eq.), DCM, 0 °C – rt, 2 h, 72%; (e) 5% TFA, DCM, 0 °C, 0.5 h; (f) DIPEA (2 eq.), toluene, reflux, 16 h, 83% (over 2 steps); (g) Na/naphthalene (1 M solution), THF, 0 °C – rt, 2 h, 50%.
comparison with an authentic sample of 2 confirmed that it was identical to our synthetic TFA salt of 2. Preliminary biological activity associated with 2 has also been reported for the first time.

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