Pergamon

Tetrahedron Letters 43 (2002) 899–902

TETRAHEDRON LETTERS

Tandem cyclisation and [2,3]-Stevens rearrangement to 2-substituted pyrrolidines

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Received 2 October 2001; revised 14 November 2001; accepted 30 November 2001

Abstract—Reaction of *N*-methylallylamine with diethyl *meso*-2,5-dibromoadipate in DMF at ambient temperature in the presence of potassium carbonate led directly to the two diastereomers of diethyl 2-allyl-*N*-methylpyrrolidine-2,5-dicarboxylate. The reaction proceeds via a [2,3]-sigmatropic Stevens rearrangement, which occurred spontaneously under the reaction conditions. This gave a higher yield under milder conditions than the traditional Stevens reaction of diethyl *N*-allylpyrrolidine-2,5-dicarboxylate with iodomethane. The sequence was a key step in the synthesis of a series of analogues of the alkaloid stemofoline.

Stemofoline **1** is an alkaloid isolated from the plant *Stemona japonica*.[1] It has attracted wide interest because of its reported insecticidal activity[2] and synthetically challenging structure.[3]

As part of a programme to synthesise structurally-simplified insecticidal compounds based on stemofoline, the fused piperazine analogues **2** were designed with three key objectives in mind (Fig. 1): (i) maintain the structural rigidity of the natural product and a good 3-D overlay of functionality; (ii) ensure the pK_a is kept close to the unusually low measured value of 6.8 for stemofoline; and (iii) incorporate an alkyl substituent to mimic the *n*-butyl side chain. The second nitrogen of the piperazine offers a handle for coupling with tetronate equivalents and the acylated nitrogen can inductively lower the pK_a of the basic nitrogen.

Appropriate tetronate[4] **3** (X = O) and tetramate[5] **3** (X = NR) coupling partners were readily prepared as both the *E* and *Z* acids using one of several effective literature routes.

Synthesis of the 3,8-diazabicyclo[3.2.1]octane ring system in coupling partner **4** was accomplished using modified literature procedures[6,7] (Scheme 1). Starting with diethyl *meso*-2,5-dibromoadipate **5**, reaction with benzylamine gave first the pyrrolidine via ring closure

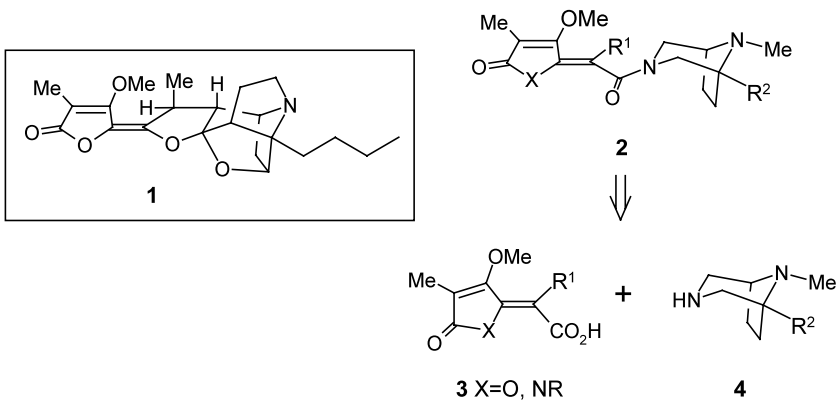

Figure 1.

Keywords: [2,3]-sigmatropic; Stevens rearrangement; stemofoline.

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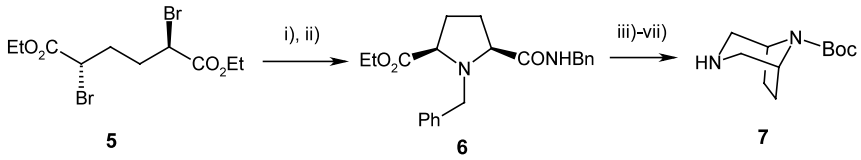


5 6 7

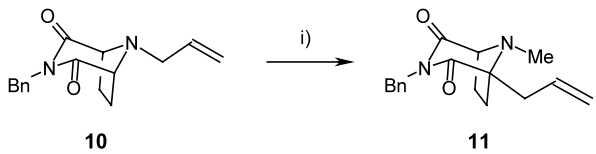
Scheme 1. *Reagents and conditions*: (i) (a) benzylamine, 3.1 equiv., toluene, 85°C, (b) filter, then evaporate; (ii) benzylamine, xylene, reflux, 71% over two steps; (iii) 230°C, neat, distil off EtOH, 73%; (iv) H_2, 1 atm, Pd/C, MeOH, HCl, 85%; (v) $LiAlH_4$, Et_2O, 0°C–reflux; (vi) $(Boc)_2O$, DCM, rt, 60% over two steps; (vii) H_2, 1 atm, Pd/C, MeOH, 72%.

and then the mono amide **6**. The minor *trans* diester was removed at this stage by column chromatography. Cyclisation was achieved by heating **6** neat to 230°C and removing ethanol.[6] Reduction with lithium aluminium hydride, *t*-butyloxycarbonyl (Boc) protection and removal of the benzyl group[7] gave **7** in a reasonable overall yield.

It was envisaged that the route to **7** could be adapted to make 1-alkyl-3,8-diazabicyclo[3.2.1]octanes **4** (R^2 = alkyl) by making use of the [2,3]-sigmatropic Stevens rearrangement[8] of a suitable intermediate. Thus, following similar initial steps, the *N*-allyl pyrrolidine **8** was prepared (Scheme 2) as a 3:1 *cis*:*trans* mixture of diesters.[9] Pyrrolidine **8** was treated under standard Stevens rearrangement conditions[8a] using excess iodomethane and potassium carbonate in DMF at 55°C for 48 h, giving a modest 42% yield of the 2-allyl pyrrolidine **9** as a 4:1 *cis*:*trans* mixture of diesters after purification. A small amount of starting material **8** was recovered, although most was consumed as polar by-products. It was postulated that the product **9** was just as likely to quaternise with iodomethane under the reaction conditions as the starting material **8**, thus lowering the overall yield.

Perhaps not surprisingly, the bicyclic system **10** gave only 2% of the [2,3]-Stevens rearrangement product **11** as well as mostly starting material, presumably because the bridgehead anion does not form very readily (Scheme 3).

A significant improvement in the [2,3]-Stevens rearrangement was achieved by considering an alternative route to the key *N*-allyl quaternary ammoniumylide via an intramolecular cyclisation rather than intermolecular quaternisation which appears to be a rate limiting step with less reactive nitrogen centres (Scheme 4). Thus, compound **5** reacts with *N*-methyl-



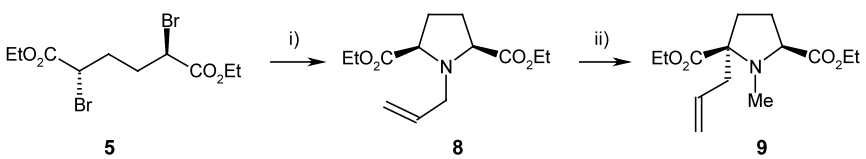
10 11

Scheme 3. *Reagents and conditions*: (i) iodomethane, K_2CO_3, 55°C, 48 h, 2% product by GC–MS.

allylamine to give the cyclised and [2,3]-Stevens-rearranged product **9** directly in one pot.[10] The [2,3]-Stevens reaction proceeds more rapidly and at lower temperature than via the quaternisation route.

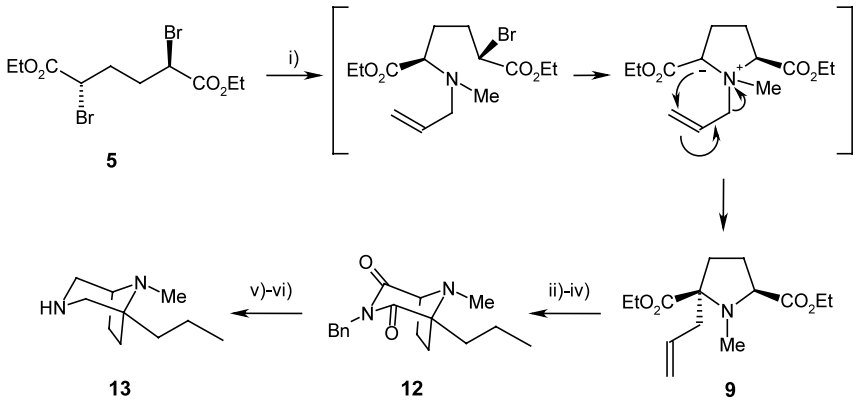
The 2-allyl pyrrolidine **9** was taken on to the 1-alkyl-3,8-diazabicyclo[3.2.1]octane following similar steps to those described to make compound **7**. The key cyclisation to **12**[11] was found to proceed much more cleanly with the *n*-propyl derivative than the allyl, so this was reduced prior to cyclisation. Only the major *cis* isomer was observed to undergo subsequent cyclisation, with isolation of the minor undesired *trans* by-product, thus confirming the initial stereochemistry. Reduction and debenzylation provided **13**[12] which was then readily coupled with a number of tetronic and tetramic acid derivatives **3**, for example **14** as shown in Scheme 5 to give the stemofoline mimic **15**.[13]

In summary, it has been demonstrated that an intramolecular cyclative approach to the key quaternary intermediate required for the [2,3]-Stevens rearrangement enables a more rapid reaction under milder conditions, leading to a significantly higher overall yield. It is expected that this reaction will find general applications in the synthesis of other 2-substituted pyrrolidines and derivatives of cyclic amines such as proline.

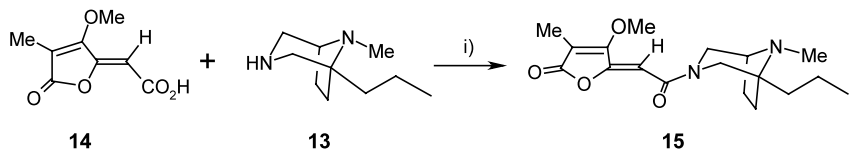


5 8 9

Scheme 2. *Reagents and conditions*: (i) allylamine, 3.1 equiv., toluene, 8°C, 80% as a 3:1 *cis*:*trans* mixture of diesters by GC; (ii) iodomethane, K_2CO_3, DMF, 55°C, 48 h, 42% as a 4:1 *cis*:*trans* mixture by GC.



Scheme 4. *Reagents and conditions*: (i) *N*-methylallylamine, K_2CO_3, DMF, 0°C–rt, 58%, as a 13:5 *cis*:*trans* mixture by GC after column chromatography; (ii) benzylamine, xylene, reflux, 48 h, 55%; (iii) H_2, Pd/C, 1 atm EtOH, quant.; (iv) 230°C, neat, distil off EtOH, 71%; (v) $LiAlH_4$, Et_2O, 0°C–reflux, 79%; (vi) H_2, 6.5 bar, Pd/C, EtOH, 35 h, 94%.



Scheme 5. *Reagents and conditions*: (i) (a) **14**, oxalyl chloride, THF, DMF (cat.), rt, 1 h; (b) **13**, Et_3N, rt, 4 h, 57%.

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9. The stereochemistry of the inseparable *cis* and *trans* diesters of pyrrolidine (**8**) was confirmed empirically by the observation that only the *cis* isomer was able to lead on to cyclisation to give the 3,8-diazabicyclo[3.2.1]octane skeleton in subsequent steps. It was possible to isolate the unreacted *trans* materials after the cyclisation reaction.
10. *Typical experimental procedure for tandem intramolecular cyclisation and Stevens rearrangement*. Preparation of compound **9**. Diethyl *meso*-2,5-dibromoadipate (11.5 g, 31.7 mmol) was dissolved in dry DMF (25 ml) and K_2CO_3 (8.75 g, 63 mmol) was added. The mixture was cooled under N_2 to 0°C (ice/water bath) with stirring and *N*-methylallylamine (2.25 g, 3.04 ml, 31.7 mmol) was added in one portion. The reaction was mildly exothermic and required cooling for 1 h, after which time it was allowed to warm to ambient temperature (25°C). After stirring for 16 h, the reaction was poured into a mixture of ether (100 ml) and water (100 ml). The aqueous phase was re-extracted with ether (100 ml). The combined organic phases were washed with water (×2), brine and dried ($MgSO_4$). Evaporation and purification by flash chromatography on silica, eluting with ethyl acetate in hexane (gradient 15–25%) gave **9** (as a 13:5 mixture of *cis*:*trans* diester isomers) as an oil 4.94 g (58%). ^{1}H NMR (270 MHz, $CDCl_3$): δ (ppm) 1.21–1.32 (6H, m), 1.70–1.82 (1H, m), 1.85–2.04 (1H, m), 2.04–2.16 (1H, m), 2.16–2.26 (1H, m), 2.36 (*trans*) and 2.56 (*cis*) (3H, 2s), 2.40–2.50 (1H, m), 2.61–2.74 (1H, m), 3.48–3.55 (*trans*) and 3.57–3.64 (*cis*) (1H, 2m), 4.07–4.20 (4H, m), 5.03–5.16 (2H, m), 5.60–5.76 (*cis*) and 5.78–5.92 (*trans*) (1H, 2m); calcd for $C_{14}H_{24}NO_4$ (MH+) 270.1705, found 270.1698.

11. Compound **12**: ^{1}H NMR (270 MHz, $CDCl_3$): δ (ppm) 0.98 (3H, t, $J=7.1$ Hz), 1.22–1.55 (2H, m), 1.55–1.67 (1H, m), 1.74 (1H, d, $J=9.2$ Hz), 1.81 (1H, d, $J=9.2$ Hz), 1.86–2.00 (1H, m), 2.10–2.30 (2H, m), 2.23 (3H, s), 3.83 (1H, d, $J=7.1$ Hz), 4.87 (2H, s), 7.20–7.47 (5H, m); (MS (ES+) 287 (MH^+); calcd for $C_{17}H_{23}N_2O_2$ (MH+) 287.1760, found 287.1760.
12. Compound **13**: ^{1}H NMR (270 MHz, $CDCl_3$): δ (ppm) 0.93 (3H, t, $J=7.1$ Hz), 1.20–1.63 (4H, m), 1.73–1.87 (1H, m), 1.94–2.20 (3H, m), 2.42 (3H, s), 2.70–2.80 (2H, m), 3.10 (1H, d, $J=12.1$ Hz), 3.31–3.39 (2H, m), 6.70 (1H, v br s); MS (ES+) 169 (MH^+).
13. Compound **15**: ^{1}H NMR (270 MHz, $CDCl_3$): δ (ppm) (2:1 rotameric isomers) 0.89–0.98 (3H, m), 1.24–1.75 (7H, m), 1.90–2.02 (1H, m), 2.11 and 2.12 (3H, 2s), 2.34 (3H, s), 2.84 (0.65H, d, $J=12.8$ Hz), 3.07–3.34 (2.7H, m), 3.58 (0.65H, d, $J=12.8$ Hz), 4.20–4.13 (1H, m), 4.17 and 4.18 (3H, 2s), 5.73 (1H, s) MS (ES+) 335 (MH^+); calcd for $C_{18}H_{27}N_2O_4$ (MH+) 335.1971, found 335.1979.