

# A general method for making bicyclic compounds with nitrogen at a bridgehead—application to the halichlorine spiro subunit†

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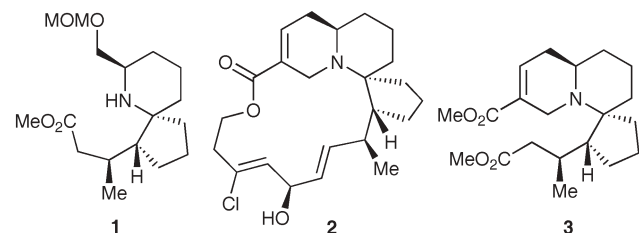
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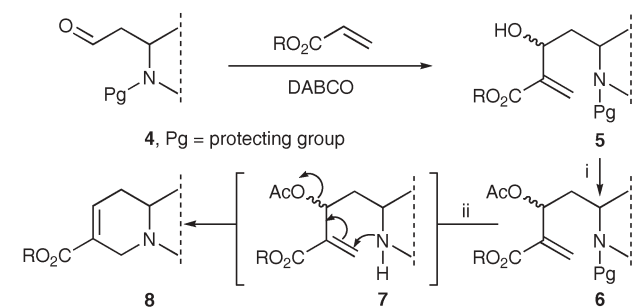
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*N*-Protected  $\beta$ -amino aldehydes having the nitrogen in a ring are easily converted into Morita–Baylis–Hillman adducts; *O*-acetylation and *N*-deprotection result in spontaneous cyclization to bicyclic structures having nitrogen at a bridgehead.

A recent report from this laboratory<sup>1</sup> described the preparation of spiro amine **1**, which was made during studies on the total synthesis of the marine natural product halichlorine (**2**).<sup>2</sup> An obvious next step was to convert **1** into **3**, and this has now been achieved through the development of a new and general method for making compounds that contain a bicyclic subunit with nitrogen at a bridgehead. The approach (Scheme 1) is based on sequential formation of Morita–Baylis–Hillman (MBH) alcohols (**4**  $\rightarrow$  **5**) and intramolecular  $S_N2'$  displacement of the derived acetates (**6**  $\rightarrow$  **7**  $\rightarrow$  **8**). In the present work we have made alcohols of type **5** by MBH<sup>3</sup> condensation (and used only acrylates), but the same compounds should also be accessible by other<sup>3,4</sup> methods.



While *O*-acetates of MBH alcohols are known to undergo intermolecular  $S_N2'$  displacement,<sup>3,5</sup> the intramolecular 6-*endo* pathway<sup>6</sup> (Scheme 1, **7**  $\rightarrow$  **8**) requires that no competing



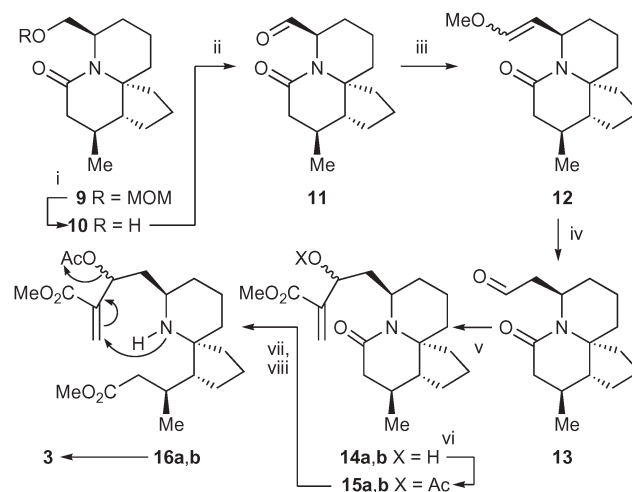
Scheme 1

† Electronic supplementary information (ESI) available: characterization data for compounds **3**, **21**, **26**, **32** and **38**. See <http://www.rsc.org/suppdata/cc/b4/b413481h/>

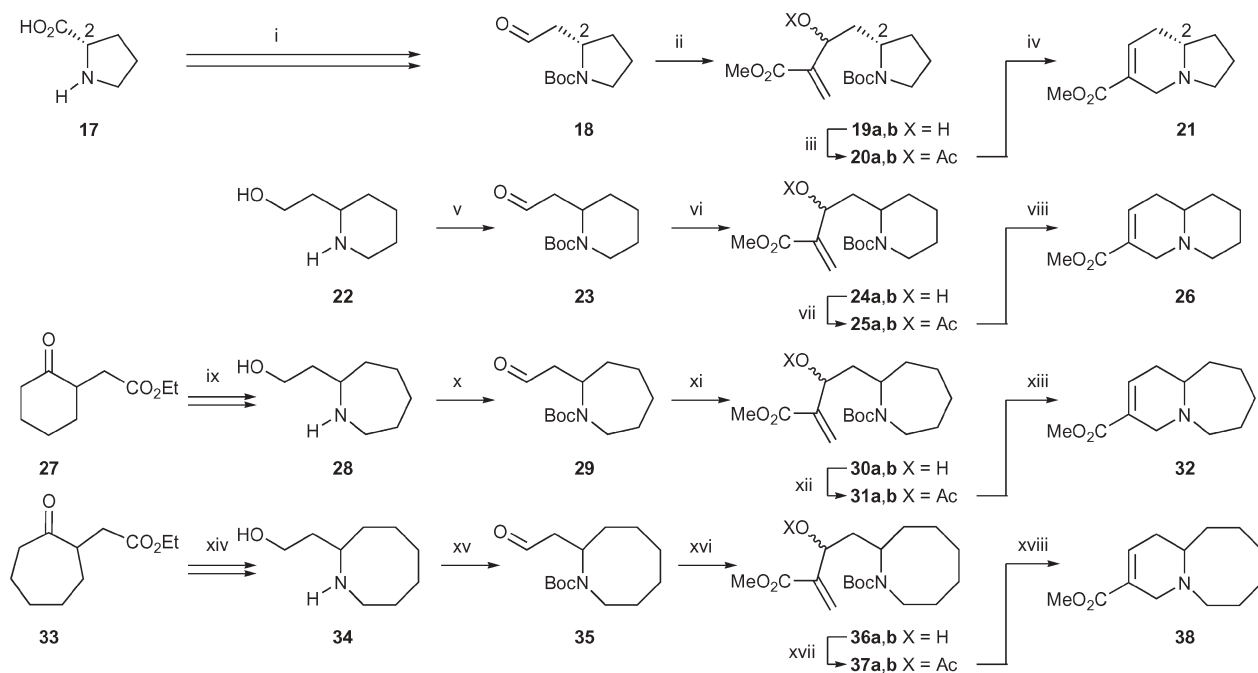
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stereoelectronic or reactivity factors intervene to direct cyclization onto the  $CO_2R$  group<sup>7</sup> of **7** or to cause *O*  $\rightarrow$  *N* acetyl transfer; in the event, the desired ring closure (**7**  $\rightarrow$  **8**) occurs smoothly.

The lactam **9**,<sup>1</sup> an intermediate in the preparation of **1**, was deprotected ( $Me_3SiBr$ , 84%, **9**  $\rightarrow$  **10**) and oxidized (Swern, 85%) to aldehyde **11**. Wittig reaction with  $Ph_3P=CH(OMe)$  and hydrolysis (CSA, aqueous MeCN) of the intermediate enol ethers then gave the expected aldehyde (**11**  $\rightarrow$  **12**  $\rightarrow$  **13**, 74% overall). When aldehyde **13**<sup>8</sup> was dissolved in methyl acrylate, condensation occurred on addition of DABCO and  $Sc(OTf)_3$ .<sup>9</sup> Although the resulting alcohols (**14a**, more polar) and **14b** (less polar) could be separated, it was more convenient to acetylate the mixture and separate the corresponding acetates **15a** (37% from **13**) and **15b** (34%). When each of the acetates **15a** and **15b** was treated with  $Me_3OBF_4$  and then with aqueous  $Na_2CO_3$ , the lactam ring was opened to amino esters **16a** and **16b**, respectively, and these cyclized *in situ* to afford the desired bis-ester **3** (77% for **15a** and 72% for **15b**).<sup>10</sup> Aldehyde **13** was recovered unchanged either after exposure to DABCO in  $CH_2Cl_2$  for 3 days, or when the MBH condensation was worked up before completion. These observations show that epimerization by retro-Michael elimination and re-addition does not occur.



**Scheme 2** Reagents and conditions: (i)  $Me_3SiBr$ ,  $CH_2Cl_2$ ,  $-10^\circ C$ , 2 h, 84%; (ii) Swern oxidation, 85%; (iii)  $MeOCH_2PPh_3Cl$ , *t*-BuOK, THF,  $0^\circ C$ , 2 h; (iv) camphorsulfonic acid, MeCN–water, 4 h, 74% over two steps; (v) methyl acrylate, DABCO,  $Sc(OTf)_3$ , 5 days; (vi)  $AcCl$ , pyridine,  $CH_2Cl_2$ ,  $0^\circ C$ , 1 h,  $25^\circ C$ , 1 h, over two steps 37% of **15a**, 34% of **15b**; (vii)  $Me_3OBF_4$ ,  $CH_2Cl_2$ , 1.5 h; (viii) 20% aqueous  $Na_2CO_3$ , MeCN, 2 h, 77% from **15a**, 72% from **15b**.



**Scheme 3** Reagents and conditions: (i) References 10–12; (ii) methyl acrylate, DABCO, 3 days, 39% (**19a**), 34% (**19b**); (iii) AcCl, pyridine, CH<sub>2</sub>Cl<sub>2</sub>, 1 h, 89% (**20a**), 85% (**20b**); (iv) CF<sub>3</sub>CO<sub>2</sub>H, CH<sub>2</sub>Cl<sub>2</sub>, 1 h; aq Na<sub>2</sub>CO<sub>3</sub>, MeCN, 1 h, 77%; (v) (a) (Boc)<sub>2</sub>O, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 1 h, room temperature, 12 h, 87%; (b) Dess–Martin periodinane, CH<sub>2</sub>Cl<sub>2</sub>, 1.5 h, 88%; (vi) as in (ii), 46% (less polar), 38% (more polar); (vii) as in (iii), 94% for **24a**, 92% for **24b**; (viii) as in (iv), 77%; (ix) (a) NaN<sub>3</sub>, aq H<sub>2</sub>SO<sub>4</sub>, 0 °C, 16 h, 74%; (b) LiAlH<sub>4</sub>, dioxane, reflux, 24 h, 80%; (x) (a) (Boc)<sub>2</sub>O, EtOAc, 16 h, 98%; (b) Swern, 2 h, 87%; (xi) as in (ii), 5 days, 39% (less polar), 47% (more polar); (xii) as in (iii), 92% for **30a**, 94% for **30b**; (xiii) as in (iv) 90% (more polar), 87% (less polar); (xiv) (a) NaN<sub>3</sub>, aq H<sub>2</sub>SO<sub>4</sub>, 0 °C, 16 h, 80%; (b) LiAlH<sub>4</sub>, THF, reflux, 24 h, 71%; (xv) (a) as in (x), 83%; (b) as in (x), 80%; (xvi) as in (ix) 49% (more polar **36a**), 45% (less polar **36b**); (xvii) as in (iii), 78% for **37a**, 79% for **37b**; (xviii) as in (iv), 84% for **37a**, 93% for **37b**.

The approach of Scheme 2 appears to be general, and we have applied it to several other cases (Scheme 3).

L-Proline (**17**) was converted by literature methods<sup>11–13</sup> into aldehyde **18**, which underwent condensation with methyl acrylate, affording a separable mixture of **19a** (more polar, 39%) and **19b** (less polar, 34%). Acetylation produced the corresponding acetates **20a** (89%) and **20b** (85%). Finally, exposure of a mixture of both acetates to CF<sub>3</sub>CO<sub>2</sub>H resulted in *N*-deprotection, at which point, treatment with aqueous Na<sub>2</sub>CO<sub>3</sub> caused spontaneous cyclization to **21** (77% yield). HPLC analysis [Chiracel OD-H, 1% EtOH–hexane] showed the material to have an enantiomeric purity of 99.8%, indicating that little, if any, racemization occurs in the synthetic sequence.

In another series of experiments, commercial (2-hydroxyethyl)piperidine (**22**) was converted by *N*-protection (Boc<sub>2</sub>O, 87%) and Dess–Martin oxidation (88%) into aldehyde **23**, which underwent efficient MBH condensation [**23** → **24a** (more polar, 38%) and **24b** (less polar, 46%)]. Once again, acetylation (94% for **24a**, 92% for **24b**), *N*-deprotection (CF<sub>3</sub>CO<sub>2</sub>H), and treatment with aqueous Na<sub>2</sub>CO<sub>3</sub> resulted in ring closure, giving **26** (77% from a mixture of both acetates).

We also investigated two other ring sizes for the starting amine. Keto ester **27** was converted by Schmidt reaction and LiAlH<sub>4</sub> reduction into **28**,<sup>14</sup> which was protected on nitrogen [Boc<sub>2</sub>O, 98%], oxidized (Swern, 87%), and subjected to the MBH condensation [**29** → **30a** (more polar, 47%) and **30b** (less polar, 39%)]. Acetylation (92% for **31a**, 94% for **31b**) and *N*-deprotection (CF<sub>3</sub>CO<sub>2</sub>H) and basification gave **32** (90% from **31a**, 87% from **31b**). Similarly, keto ester **33** was converted into amino alcohol **34**

and then into aldehyde **35**. Our standard sequence (**35** → **36a,b**, → **37a,b**, → **38**) then proceeded in the expected way.

In summary, synthetic work related to halichlorine has led to the development of a method for generating bicyclic amines with nitrogen at a bridgehead. The process occurs with preservation of stereochemistry  $\alpha$  to the nitrogen.

All new compounds were fully characterized by spectroscopic methods, including high resolution mass spectrometry. We thank NSERC for financial support and C. Boucher [Boehringer Ingelheim (Canada)] for ee measurements. M.Y. holds a Province of Alberta Graduate Fellowship.

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