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An efficient route to all eight stereoisomers of a tri-functionalised cyclopentane scaffold for drug discovery

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Abstract—A route to all eight stereoisomers of 3-(*tert*-butoxycarbonylamino)-4-hydroxycyclopentanecarboxylic acid methyl ester is presented; these products should prove to be valuable scaffolds in pharmaceutical discovery.

1. Introduction

3-(*tert*-Butoxycarbonylamino)-4-hydroxycyclopentanecarboxylic acid methyl esters are conformationally rigid and potentially valuable scaffolds for pharmaceutical discovery.[1] We have recently described an approach to these targets that is primarily concerned with the selectivity of hydrogenation reactions on cyclopent-1-enecarboxylate intermediates.[2] Epoxidations with Oxone® were employed to introduce the oxygen functionality, but we encountered poor volume efficiency and low yields which restricted the commercial utility of this approach. We now present a new route that proceeds by way of a stereodefined bromocyclisation, enabling the individual synthesis of any of the eight isomers **1a**–**1h** (Fig. 1) by methods that are industrially scaleable.

2. Results and discussion

The synthesis starts with the bioresolution of the racemic bicyclic lactam 2-azabicyclo[2.2.1]hept-5-en-3-one **2**,[3] a process that we have operated at multi-tonne scale since the single isomer is a valuable synthon for carbocyclic nucleoside production.[4] By use of complementary enzymes, both enantiomers of the lactam are now commercially available,[5] though here we also utilise the amino acid formed in the bioconversion. Thus, aminoester **3a** was obtained from the homochiral lactam in 98% overall yield by treatment with thionyl chloride in methanol and subsequent *tert*-butoxycarbonyl derivatisation of the intermediate hydrochloride salt. Its enantiomer **3b** was obtained analogously from the amino acid in 82% overall yield (Scheme 1).

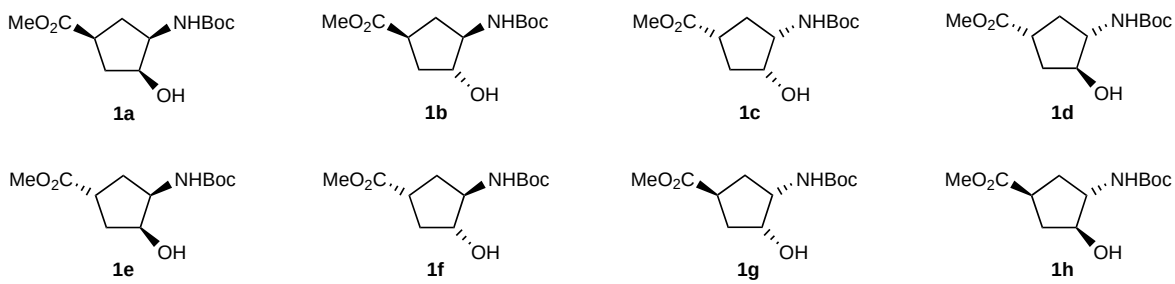

Figure 1.

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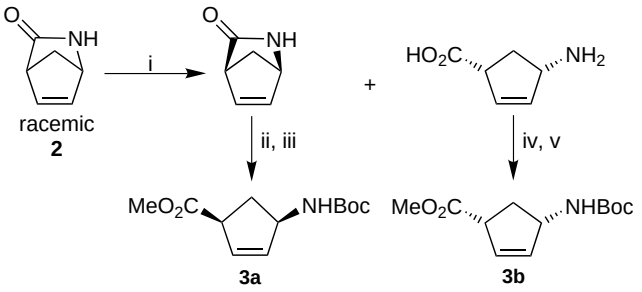
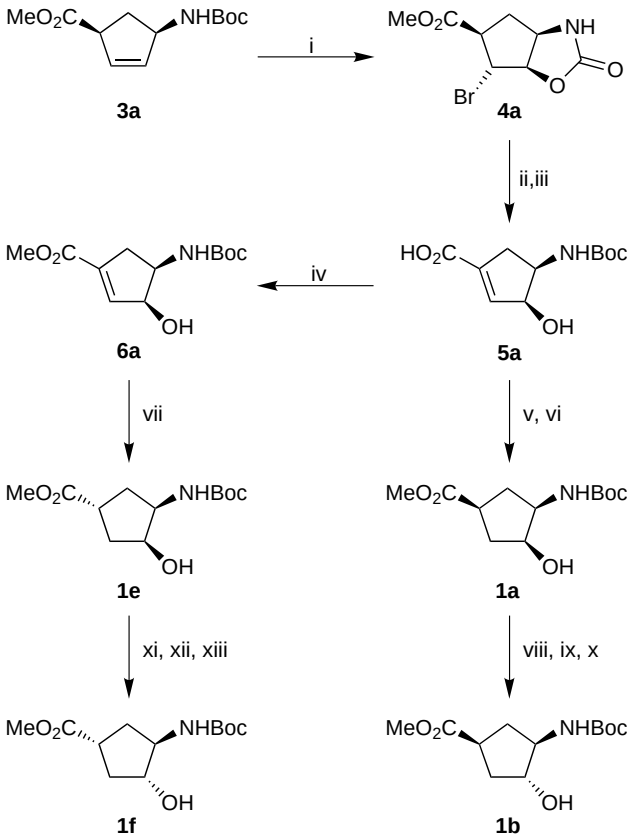


Scheme 1. *Reagents and conditions*: (i) lactamase; (ii) $SOCl_2$, MeOH, 14 h, 0°C then room temp., 100%; (iii) (*tert*-$BuO_2C)_2O$, NEt_3, CH_2Cl_2, 2 h, 0°C, 98%; (iv) $SOCl_2$, MeOH, 2 h, 0°C then room temp., 85%; (v) (*tert*-$BuO_2C)_2O$, NEt_3, CH_2Cl_2, 2 h, 0°C, 96%.

Cyclopentene **3a** was subjected to an NBS-promoted bromocyclisation, whereby formation of a cyclic carbamate **4a** in high yield introduced the oxygen atom with defined stereochemistry.[6] Its treatment with alkali effected elimination of HBr and the hydrolysis of both the ester and carbamate functions. *tert*-Butoxycarbonylation in situ gave the key intermediate **5a** as a white solid in an overall 80% yield from **3a** (Scheme 2). While the hydrobromide elimination removes a stereocentre, it gives the opportunity to form either of two new isomers by way of stereodirected hydrogenation. Usefully, hydrogenation over palladium on charcoal delivered hydrogen to the least hindered olefin face to provide the all *cis*-stereoisomer with a d.e. of 76% in a yield of 98%. The purity could be raised by formation of the *tert*-butylamine salt giving a d.e. of 98% in 65% yield, which was then esterified using methyl chloroformate in methanol to provide the requisite scaffold **1a** in 92% as a colourless oil. Its enantiomer **1c** was generated using an identical synthetic sequence from **3b**. In contrast, homogeneous hydrogenation in the presence of catalytic (*R*,*R*)-{[MeDuPHOS]-Rh(COD)}BF_4[7] gave the opposite stereoisomer. Hydrogenation was sluggish using the carboxylic acid **5a**, attributed to unproductive co-ordination of the carboxylic acid function with the rhodium catalyst,[8] but with ester **6a** reaction was rapid giving **1e** (d.e. 98, 100%).[2] Likewise the opposite enantiomer **1g** was obtained from the **3b** derived allylic alcohol using the (*S*,*S*)-catalyst. The scope of this high selectivity, which we attribute to secondary coordination to the catalyst from the butoxycarbonylamino functionality, has been explored separately.[2]

Access to the scaffolds having the hydroxyl function in a *trans*-relationship to the amino function **1b**, **1d**, **1f** and **1h** was easily gained via a mesylation–acetate displacement inversion sequence performed on **1a**, **1c**, **1e** and **1g** using standard procedures. Scaffolds **1b**, **1d**, **1f** and **1h** were isolated as white solids in 81–83% overall yields. The absolute stereochemistry of all scaffolds is assumed to be related to that of lactam **2**.[9] The relative stereochemistry of scaffolds **1a**, **1b**, **1e** and **1f** was determined by NOE experiments performed on the respective *O*-acetylated derivatives. ^1H NMR spectral data for **1d** are in agreement with those previously reported.[10]



Scheme 2. *Reagents and conditions*: (i) NBS, THF–H_2O (10:1), room temp., 18 h, 95%; (ii) KOH, MeOH–H_2O (1:1), 90°C, 3 days; (iii) (*tert*-$BuO_2C)_2O$, H_2O–THF (5:1), pH 10.5, 5°C to room temp., 18 h, 84% (overall for steps (ii) and (iii)); (iv) MeOCOCl, NEt_3, MeOH, 5°C then room temp., 18 h, 81%; (v) H_2 (35 psi), Pd/C, MeOH, room temp., 18 h (d.e. 76%, 98%); (vi) MeOCOCl, NEt_3, MeOH, 5°C then room temp., 18 h, 86%; (vii) H_2 (75 psi) {(*R*,*R*)-[MeDuPHOS]-Rh(COD)}BF_4, MeOH, room temp. (d.e. >97%, 100%); (viii) $MeSO_2Cl$, TEA, DMAP, CH_2Cl_2, 5°C, 3 h, 97%; (ix) KOAc, DMF, 60°C, 48 h, 85%; (x) NaOMe, MeOH, 5°C, 7 h, 98%; (xi) $MeSO_2Cl$, TEA, DMAP, CH_2Cl_2, 5°C, 5 h, 94%; (xii) KOAc, DMF, 60°C, 8 days, 88%; (xiii) NaOMe, MeOH, 5°C, 6 h, 98%.

3. Conclusion

We have demonstrated a scaleable synthesis of all eight stereoisomers of a scaffold useful for the pharmaceutical industry. Interestingly, halogenated products derived from scaffold **1d** have been shown to be potent conformationally rigid deactivators of γ-aminobutyric acid aminotransferase.[10]

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