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# The design of efficient and selective routes to a key 1,4-*cis*-substituted cyclohexylamide intermediate

Christopher Barfoot [a], Gerald Brooks [b], David T. Davies [b], John Elder [a], Ilaria Giordano [a], Alan Hennessy [a,*], Graham Jones [b], Roger Markwell [b], Michael McGuire [c], Timothy Miles [a], Neil Pearson [d], Grant Spoors [c], Ravinder Sudini [c], Hengxu Wei [c], Jeffery Wood [c]

[a] Antibacterial Discovery Performance Unit, Infectious Diseases CEDD, GlaxoSmithKline, Gunnels Wood Road, Stevenage SG1 2NY, UK
[b] Antibacterial Discovery Performance Unit, Infectious Diseases CEDD, GlaxoSmithKline, Third Avenue, Harlow CM19 5AW, UK
[c] Synthetic Chemistry, GlaxoSmithKline, 709 Swedeland Road, King of Prussia, PA 19406, USA
[d] Antibacterial Discovery Performance Unit, Infectious Diseases CEDD, GlaxoSmithKline, 1250 South Collegeville Road, Collegeville, PA 19426, USA

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ABSTRACT

This Letter describes the synthetic challenges in synthesising key 1,4-*cis*-substituted cyclohexylamide intermediate **1** for our research programme. Five different routes address the major issues of selectivity to afford the *cis* product in isomerically pure form and in high yield. Major purification issues were also encountered upon scaling some of the routes. The merits of the diverse routes are assessed and the reasoning given for which one was ultimately used for large-scale synthesis of **1**.



During the synthesis of a series of compounds for an anti-bacterial medicinal chemistry programme, we encountered the need for bulk supplies of the key 1,4-*cis*-substituted cyclohexylamide **1**.[1]

This compound or its immediate precursors were unknown in the literature.[1] This was unlike its des-hydroxy analogue **2**, which was readily obtained by standard amide formation from the commercially available carboxylic acid **3** (Fig. 1).[2]

For initial supplies of compound **1**, we decided to use ketone **4** as a starting material as shown in Scheme 1. Conversion into the hydroxy-amide by reaction with KCN and then treatment with a strong acid gave **5** with poor selectivity. Subsequent re-protection and purification by chromatography gave **1**.

This synthetic approach was attractive since it required only a few steps from a readily available starting material. The overall yield was modest (8%), but the major problem was that the sequence could not be adequately scaled up. Chromatography of the close running *cis* and *trans* isomers was extremely difficult and made large-scale processing impractical. Recrystallisation of this mixture also proved fruitless and after considerable efforts at optimisation, this route was abandoned.

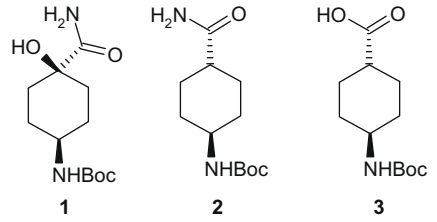
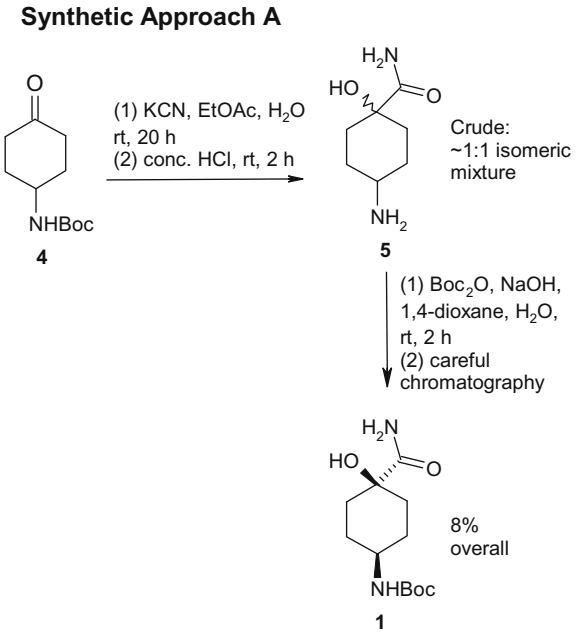



**Figure 1.** Structure of **1** and related compounds.




**Scheme 1.** Synthetic approach A.

* Corresponding author. Tel.: +44 1438762654.
*E-mail address:* alan.j.hennessy@gsk.com (A. Hennessy).

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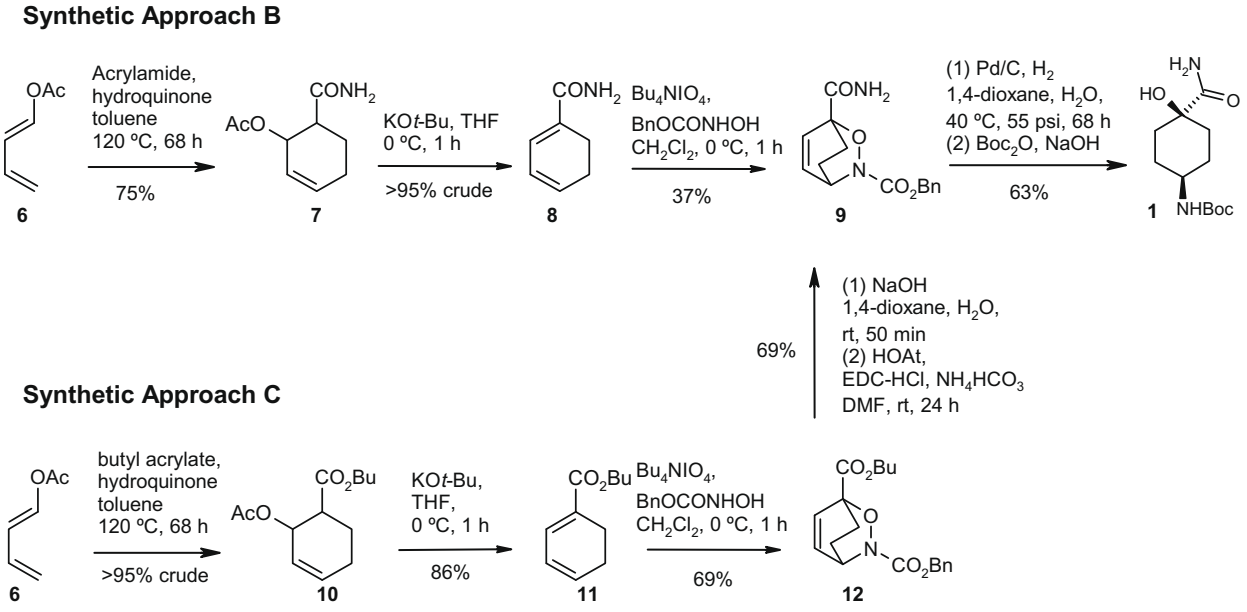
In order to obtain larger supplies of compound **1**, we decided to employ a different approach in which we hoped to fix the stereochemistry and therefore avoid the tedious chromatography step. This approach relied on a standard Diels–Alder strategy to reach substituted diene **8** and then a hetero Diels–Alder reaction to give **9**. This approach has some literature precedent and seemed to us an ideal way of forming compound **1**.[3]

As can be seen in Scheme 2, the initial sequence to diene **8** proceeded in excellent yield, unfortunately, the subsequent hetero Diels–Alder reaction occurred in a very moderate 37% yield to give compound **9**. The hetero Diels–Alder reaction of ester **11** worked considerably better than that of amide **8**, but then, two more steps were required to access common intermediate **9**. Subjecting **9** to forcing hydrogenation conditions followed by Boc-protection gave the desired *cis* stereochemically pure compound **1**.

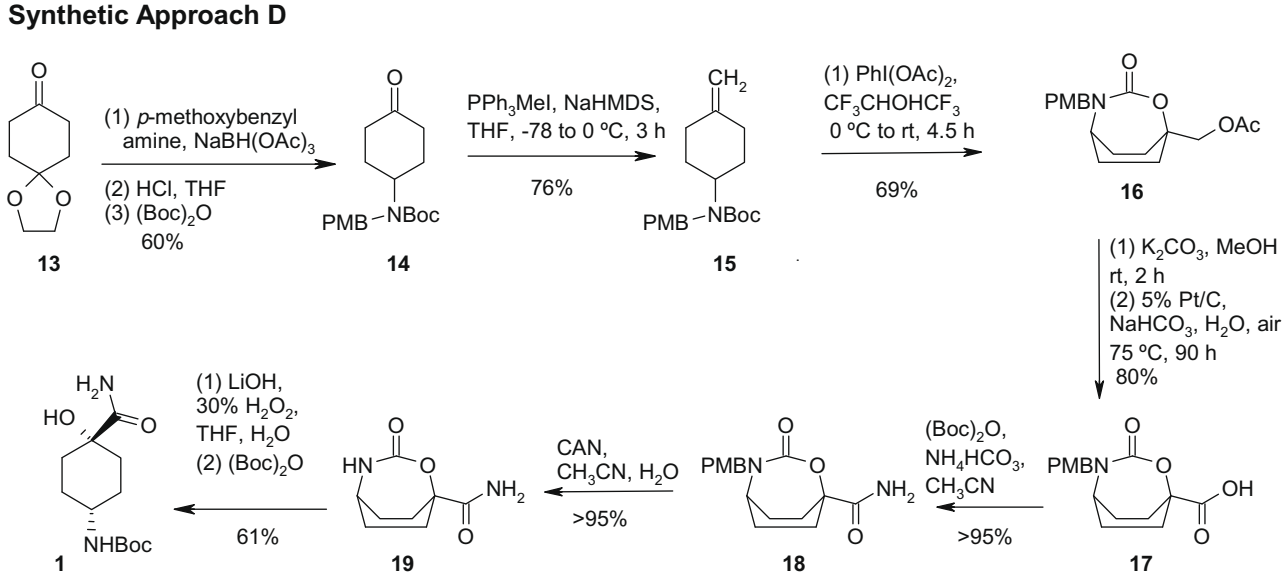
Although synthetic approaches B and C were successful in their aims to give a scalable route, one problem was that the forcing hydrogenation conditions resulted in partial hydrogenolysis of the tertiary alcohol formed from **9**. Therefore small amounts (1–10%) of compound **2** were contaminating the product and leading to downstream chemistry issues. This impurity was not removable by recrystallisation but rather required intensive chromatography. As with synthetic approach A, this was not suitable for a large-scale processing.

Another approach which would control the *cis* stereochemistry is described in Scheme 3 and relies on a hypervalent iodine induced cyclisation.[4]

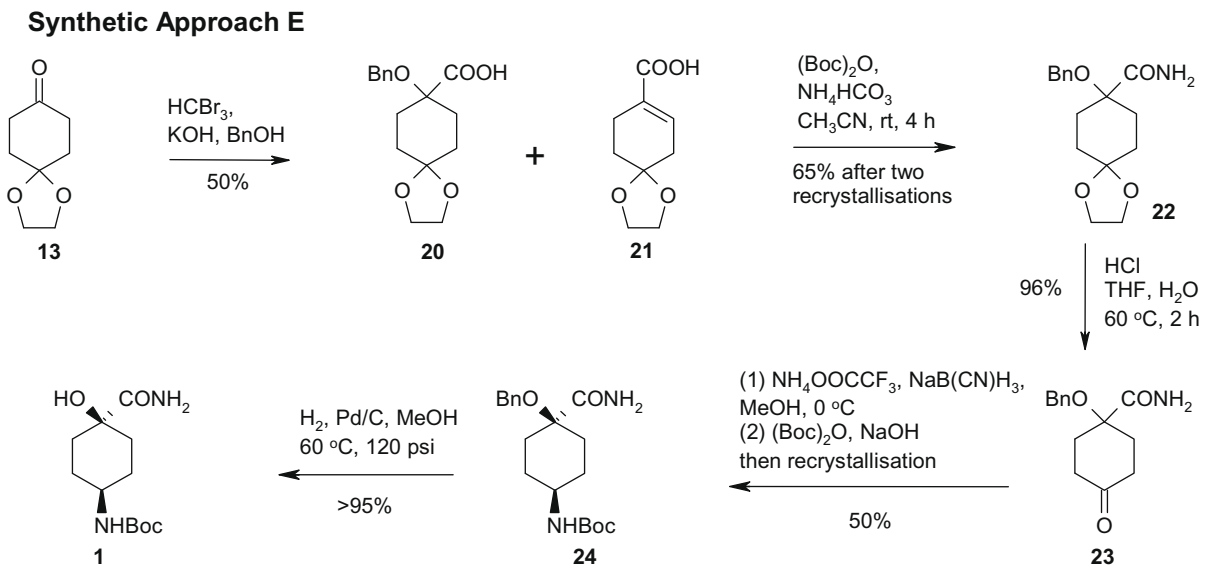
Starting from the commercially available **13**, the key intermediate **15** was produced using standard chemistry. To our delight, treatment of **15** with diacetoxy iodobenzene induced the desired




**Scheme 2.** Synthetic approaches B and C.




**Scheme 3.** Synthetic approach D.




**Scheme 4.** Synthetic approach E.

**Table 1**
Comparison of the synthetic approaches

| Approach | Number of steps | Overall yield (%) |
|---|---|---|
| **A** | 3 | 8 |
| **B** | 5 | 17 |
| **C** | 7 | 26 |
| **D** | 8 | 15 |
| **E** | 5 | 16 |

intramolecular cyclisation to give the intermediate acetoxy compound **16** in good yield and purity. Standard manipulation of the acetate to a primary amide over three steps led to **18**. Removal of the PMB group, cleavage of the carbamate, followed by a final Boc-protection step led to the desired compound **1**.

This route had none of the problems of *cis*/*trans* selectivity and also had no issues with hydrogenolysis of the tertiary alcohol functionality.

Synthetic approach E adopted a different strategy and relied on introducing the *cis* stereochemistry at a late stage. Starting from readily available cyclohexanedione monoethylene ketal **13**, we decided to pursue a variant of the chemistry reported by the Kusumi group.[5] Thus the reaction of **13** with bromoform and potassium hydroxide in benzyl alcohol led to **20** in good yield along with ~5% of by-product **21**. Interestingly, when water was used as the solvent, we did not isolate any hydroxy-acid but instead only undesired **21**. Conversion of the carboxylic acid **20** into amide **22** and then deprotection to give ketone **23** proceeded smoothly. The key reductive amination reaction was then performed, followed by Boc-protection to give **24**. This reductive amination step took some optimisation and the best *cis*/*trans* ratio of 3:1 was eventually achieved under the conditions shown in Scheme 4.[6] We then discovered that *cis* **24** could be readily separated from its *trans* isomer by recrystallisation from methanol. Hydrogenation under forcing conditions cleaved the benzyl group to give the desired compound **1**.

Interestingly, this final hydrogenation did not give any of the undesired hydrogenolyis product **2** (<20 ppm), presumably because the hydrogenation in Scheme 2 goes through a potentially more labile allylic alcohol intermediate.

In Table 1, the competing approaches are compared. Although approaches A–C have a reasonably low number of steps, the technical difficulties of removing the various impurities precluded further development. Approaches D and E have similar overall yields but with only five steps, approach E was readily scaled up to deliver multi-gram quantities of compound **1**.[7]

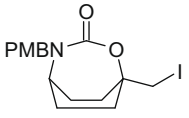
In conclusion, the challenge of making *cis* α-hydroxy amide **1** led to several approaches being investigated to install the key functionalities.

## Acknowledgements

We are grateful to Steve Richards for NMR support, Bill Leavens for mass spectroscopy support and all the chemists who have been involved in this work.

## References and notes

1. Full name for **1**: 1,1-dimethylethyl[*cis*-4-(aminocarbonyl)-4-hydroxycyclohexyl]carbamate. For the syntheses of these compounds and experimental details for the reactions in Schemes 1 and 2, see: (a) Brooks, G.; Davies, D. T.; Jones, G. E.; Markwell, R. E.; Pearson, N. D.; WO 2003087098; *Chem. Abstr.*; **2003**, *139*, 337959; (b) Axten, J. M.; Daines, R. A.; Davies, D. T.; Gallagher, T. F.; Jones, G. E.; Miller, W. H.; Pearson, N. D.; Pendrak, I.; WO 2004002992; *Chem. Abstr.*; **2004**, *140*, 94053.
2. For a synthesis, see: Ref. 1(b), example 3(a).
3. (a) Keck, G.; Fleming, S. *Tetrahedron Lett.* **1998**, *39*, 2059; (b) Martin, S.; Hartmann, M.; Josey, J. *Tetrahedron Lett.* **1998**, *39*, 2059; (c) Sirisoma, N.; Johnson, C. *Tetrahedron Lett.* **1998**, *39*, 2059.
4. (a) De Mico, A.; Margarita, R.; Mariani, A.; Piancatelli, G. *Chem. Commun.* **1997**, 1237; (b) De Mico, A.; Margarita, R.; Mariani, A.; Piancatelli, G. *Tetrahedron Lett.* **1996**, *37*, 1889; (c) Moriarty, R.; Vaid, R.; Koser, G. *Synlett* **1990**, 365. Treatment of **15** with iodine ($I_2$, $NaHCO_3$, MeCN, rt, 20 h) led to the product **25** (below) in 80% yield. However, all attempts at elaboration of **25** to carboxylic acid **17** failed.




**25**

5. Yabuuchi, T.; Kusumi, T. *Chem. Pham. Bull.* **1999**, *47*, 684–686.
6. Marui, S.; Yamamoto, T.; Sudo, K.; Akimoto, H.; Kishimoto, S. *Chem. Pharm. Bull.* **1995**, *43*, 588.
7. Data for **1**: white solid; mp 210–213 °C; $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ = 1.38 (s, 9H), 1.42–1.60 (m, 6H), 1.65–1.74 (m, 2H), 3.11–3.22 (m, 1H), 4.89–5.07 (m, 1H), 6.72 (br d, $J$ = 9 Hz, 1H), 7.01 (br s, 1H), 7.16 (br s, 1H). $^{13}$C NMR (151 MHz, DMSO-$d_6$): $\delta$ = 27.4, 28.3, 33.0, 48.6, 72.2, 77.3, 155.1, 179.5. ESI-HRMS: $m/z$ calcd for $C_{12}H_{22}N_2O_4Na$: 281.1477; found 281.1477 $[M+Na]^+$.