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An Efficient Scalable Route for the Synthesis of Enantiomerically Pure *tert*-Butyl-(1*R*,4*S*,6*R*)-4-(hydroxymethyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate

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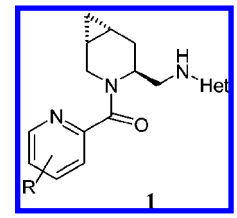
Abstract:

An efficient scalable route to synthesize the enantiomerically pure *tert*-butyl-(1*R*,4*S*,6*R*)-4-(hydroxymethyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate is described. Compared to the original routes, significant improvements were made by using an innovative approach starting from commercially available chiral lactone. In this approach, one of the key steps described is an elegant epimerization/hydrolysis of the undesired diastereoisomer avoiding tedious purification. The chemistry has been scaled up to produce kilogram amounts of *tert*-butyl-(1*R*,4*S*,6*R*)-4-(hydroxymethyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate in 43% yield over nine chemical transformations.

Introduction

The orexin ligand and receptor system have been well characterized since their discovery.[1] From these studies it has become clear that orexin receptors play a number of important physiological roles in mammals and open up new avenues for therapeutic treatments for a variety of diseases and CNS disorders. Also, the role of the orexin system in sleep and wakefulness is now well established.[2] The orexin receptors antagonists may therefore be useful in the treatment of sleep disorders including insomnia. Studies with orexin receptor antagonists in rats[3] and more recently dogs and humans further support this. Therefore a substantial amount of work has been reported by our Medicinal Chemistry colleagues,[4] as well as by others, aimed at identifying new chemical entities **1** possessing orexin antagonist activity. Due to the promising activity of compounds **1** as an orexin antagonist and the complexity of the molecules bearing the same structural motif, relatively large amounts for several of these compounds were requested for toxicological testing and clinical evaluation.



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Structurally, the complex target molecules **1** consist of constraint piperidine moiety bearing a methanamino heterocyclic subunit and a carboxylic acid linked via an amide bond (Scheme 1).

This paper describes the development of an efficient scalable synthesis of 3-azabicyclo[4.1.0]heptane ring system, **4**, key intermediate to reach the targeted molecules, **1**.

Background

The Medicinal Chemistry approach to synthesize the candidate molecules, **1**, is briefly described in Scheme 2. Commercially available (2*S*)-2-amino-4-pentenoic acid, **5**, was reduced with lithium aluminum hydride, and the amino group was then selectively protected as tosyl amide by reaction with tosyl chloride to provide **6**. Subsequent TBDPS protection of the primary alcohol and allylation of tosylamide using allyl bromide and cesium carbonate in DMF afforded **7**. Ring-closing metathesis (RCM)[5] of **7** in the presence of Grubbs I catalyst[6] in dichloromethane gave the dehydropiperidine **8** in good yield. The next step involved Simmons−Smith cyclopropanation as the key reaction to reach the desired [4.1.0] moiety using the modified conditions described by Yang et al.[7] In fact, reaction of olefin **8** in the presence of diethylzinc, trifluoroacetic acid, and diiodomethane led to the formation of the desired compound

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(1) (a) Sakurai, T.; Amemiya, A.; Ishii, M.; Matsuzaki, I.; Chemelli, R. M.; Tanaka, H.; Williams, S. C.; Richardson, J. A.; Kozlowski, G. P.; Wilson, S.; Arch, J. R. S.; Buckingham, R. E.; Haynes, A. C.; Carr, S. A.; Annan, R. S.; McNulty, D. E.; Liu, W. S.; Terrett, J. A.; Elshourbagy, N. A.; Bergsma, D. J.; Yanagisawa, M. *Cell* **1998**, *92*, 573–585. (b) Smart, D.; Jerman, J. C.; Brough, S. J.; Rushton, S. L.; Murdock, P. R.; Jewitt, F.; Elshourbagy, N. A.; Ellis, C. E.; Middlemiss, D. N.; Brown, F. *Br. J. Pharmacol.* **1999**, *128*, 1–3. (c) Willie, J. T.; Chemelli, R. M.; Sinton, C. M.; Yanagisawa, M. *Annu. Rev. Neurosci.* **2001**, *24*, 429–458. (d) Sakurai, T. *Nat. Rev. Neurosci.* **2007**, *8*, 171–181. (e) Ohno, K.; Sakurai, T. *Front. Neuroendocrinol.* **2008**, *29*, 70–87.

(2) (a) Chemelli, R. M.; Willie, J. T.; Sinton, C. M.; Elmquist, J. K.; Scammell, T.; Lee, C.; Richardson, J. A.; Williams, S. C.; Xiong, Y.; Kisanuki, Y.; Fitch, T. E.; Nakazato, M.; Hammer, R. E.; Saper, C. B.; Yanagisawa, M. *Cell* **1999**, *98*, 437–451. (b) Lee, M. G.; Hassani, O. K.; Jones, B. E. *J. Neurosci.* **2005**, *25*, 6716–6720. (c) Piper, D. C.; Upton, N.; Smith, M. I.; Hunter, A. J. *Eur. J. Neurosci.* **2000**, *12*, 726–730. (d) Smart, D.; Jerman, J. C. *Pharmacol. Ther.* **2002**, *94*, 51–61.

(3) Smith, M. I.; Piper, D. C.; Duxon, M. S.; Upton, N. *Neurosci. Lett.* **2003**, *341*, 256–258.

(4) Amantini, D.; Alvaro, G.; Di Fabio, R.; Castiglioni, E.; Pavone, F. PCT/EP2009/066017, 2009.

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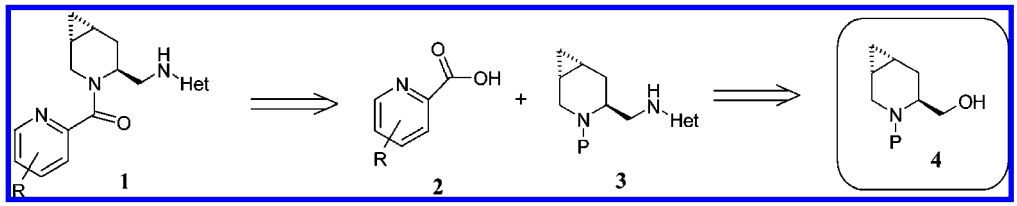
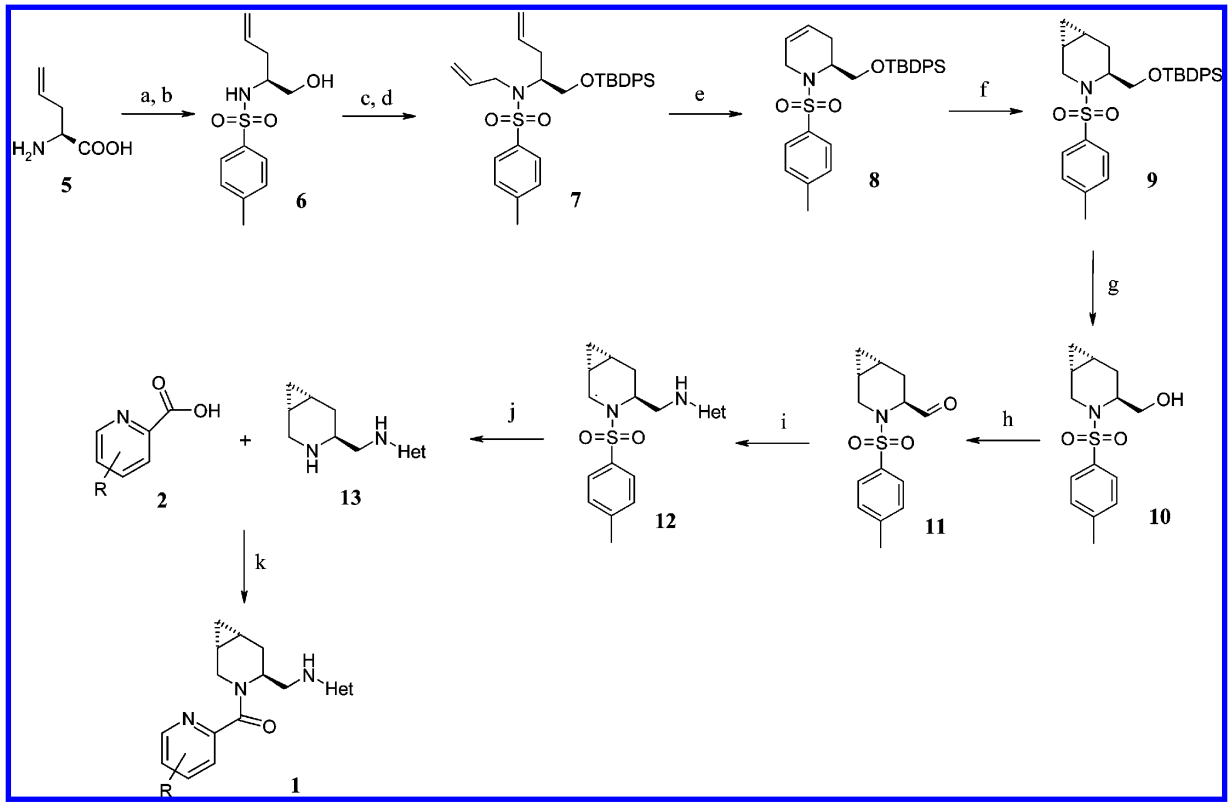
Scheme 1. **Retrosynthetic approach to molecule 1**



Scheme 2. **Medicinal chemistry route**[a]

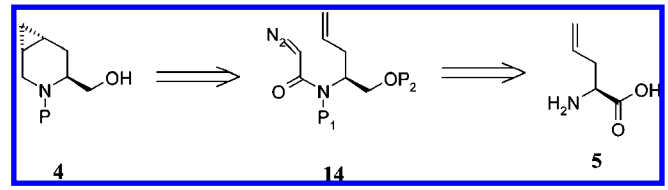


[a] Reagents and conditions: a) $LiAlH_4$, THF; b) TsCl, Na_2CO_3, H_2O/EtOAc/THF; c) TBDPSCl, imidazole, DMF; d) allyl bromide, Cs_2CO_3, DMF; e) Grubbs I, DCM; f) Et_2Zn/TFA/CH_2I_2, DCM; g) TBAF, THF; h) Dess−Martin, DCM; i) Amino-Het, $NaBH(OAc)_3$, AcOH, THF; j) Na, naphthalene, THF, −78 °C; k) TBTU, DIPEA, DCM (24% overall yield).

9 as a single diastereoisomer. Despite an excess of reagents (8−20 equiv) that was necessary to ensure full conversion of the olefin, only a modest yield (∼70%) was obtained. After TBDPS deprotection, alcohol **10** was oxidized to the corresponding aldehyde **11** using Dess−Martin reagent. Reductive amination of aldehyde **11** with sodium triacetoxyborohydride in the presence of a substituted amino heterocyclic compound gave **12** in moderate yield. The tosyl group cleavage of **12** by sodium naphthalenide in THF followed by amide coupling with the carboxylic acids **2**, using TBTU as coupling reagent, afforded **1**.

Despite the excellent diastereoselectivity during the cyclopropanation, the Medicinal Chemistry Support chemists identified several key issues. In particular, Simmons−Smith cyclopropanation required an excess of reagents (up to 20 equiv), and the yield was not reproducible. Furthermore, the removal of the tosyl group and the use of Dess−Martin were not practically suitable for a scale-up.

Scheme 3. **Rhodium-catalyzed cyclopropanation retrosynthetic route**



Medicinal Chemistry Support Synthesis. The Medicinal Chemistry Support chemists decided to investigate alternative routes to access to the [4.1.0] system. The new diastereoselective synthesis was based on intramolecular rhodium-catalyzed cyclopropanation of intermediate **14** (Scheme 3).

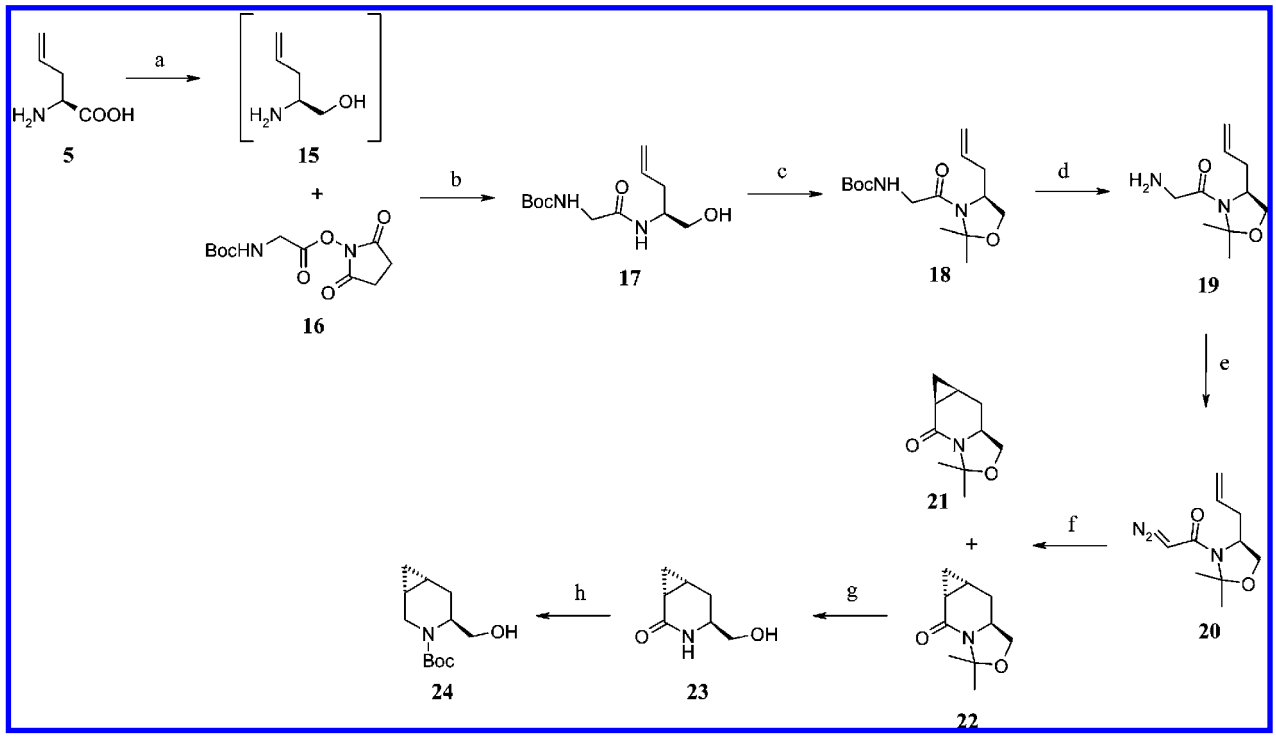
As shown in Scheme 4, the allyl diazoamide **14** is constructed again from (2*S*)-2-amino-4-pentenoic acid **5.** Reduction of **5** with lithium aluminum hydride and subsequent amidation

(5) For reviews on RCM, see: (a) Samojłowicz, C.; Bieniek, M.; Grela, K. *Chem. Rev.* **2009**, *109*, 3708–3742. (b) Vougioukalakis, G. C.; Grubbs, R. H. *Chem. Rev.* **2010**, *110*, 1746–1787. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043. (d) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073–2077. (e) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371–388. (f) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450.

(6) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039–2041.

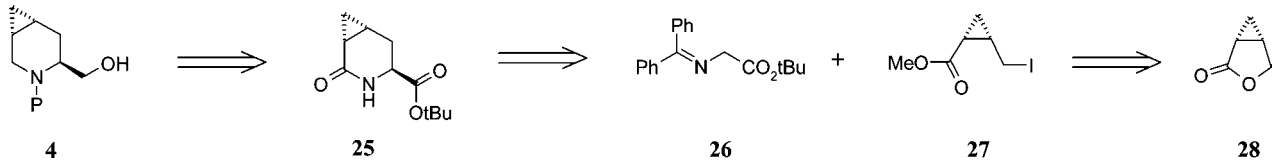
(7) Yang, Z.; Lorenz, J. C.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 8621–8624.

Scheme 4. **Medicinal chemistry support route**[a]



[a] Reagents and conditions: a) $LiAlH_4$, THF; b) 16, THF/MeOH; c) 2,2-dimethoxypropane, pTSA, toluene; d) TMSOTf, DCM, 2,6-lutidine; e) $NaNO_2$, DCM/buffer pH = 5; f) $Rh_2(OAc)_4$, DCM; g) HCl; h) BH_3 in THF, reflux, then Boc_2O, NaOH (6% overall yield).

Scheme 5. **Chemical development retrosynthetic approach**



of the resulting primary amine **15** with the commercially available Boc-Gly-OSu **16** gave **17**. To have more constraint on the carboskeleton in the key step and a relative stable protective group, the amido alcohol **17** was protected as acetonide by reaction with 2,2-methoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid, affording **18** in good yield after column chromatography. After Boc deprotection, the amine **19** was converted into the corresponding diazoamide **20**. Diazoamide **20** was treated with $Rh_2(OAc)_4$ in dichloromethane at room temperature to afford a mixture of **21** and **22** in moderate yield in 1:1 ratio.

Interestingly, switching the catalyst in the above condition to Rh_2(5*S*-MEPY)$_4$ or Rh_2(5*R*-MEPY)$_4$ did not give improvement on the diastereoselectivity of the reaction. In fact, both catalysts afforded mainly the undesired diastereoisomer **21** (ratio **21**/**22** 7:3).

After acetonide removal, reduction of **23** with borane at reflux followed by protection of the resulting secondary amine with *tert*-butoxycarbonyl group and purification by column chromatography provided the key scaffold **24**.

As evidenced in both routes, there were several key issues to be considered before envisaging a scale-up process:

(i) Safety issues: use of excess of reagents in Simmons−Smith cyclopropanation (possible problem during the work-up), use of sodium naphthalenide at low temperature (note: other amino protective group have been tried such as Boc, Cbz, but no reaction took place under cyclopropanation conditions), and hazards associated with diazochemistry.

(ii) Several chromatographic purifications were required.

(iii) Low overall yield (Medicinal Chemistry route 24%, and Medicinal Chemistry Support 6%).

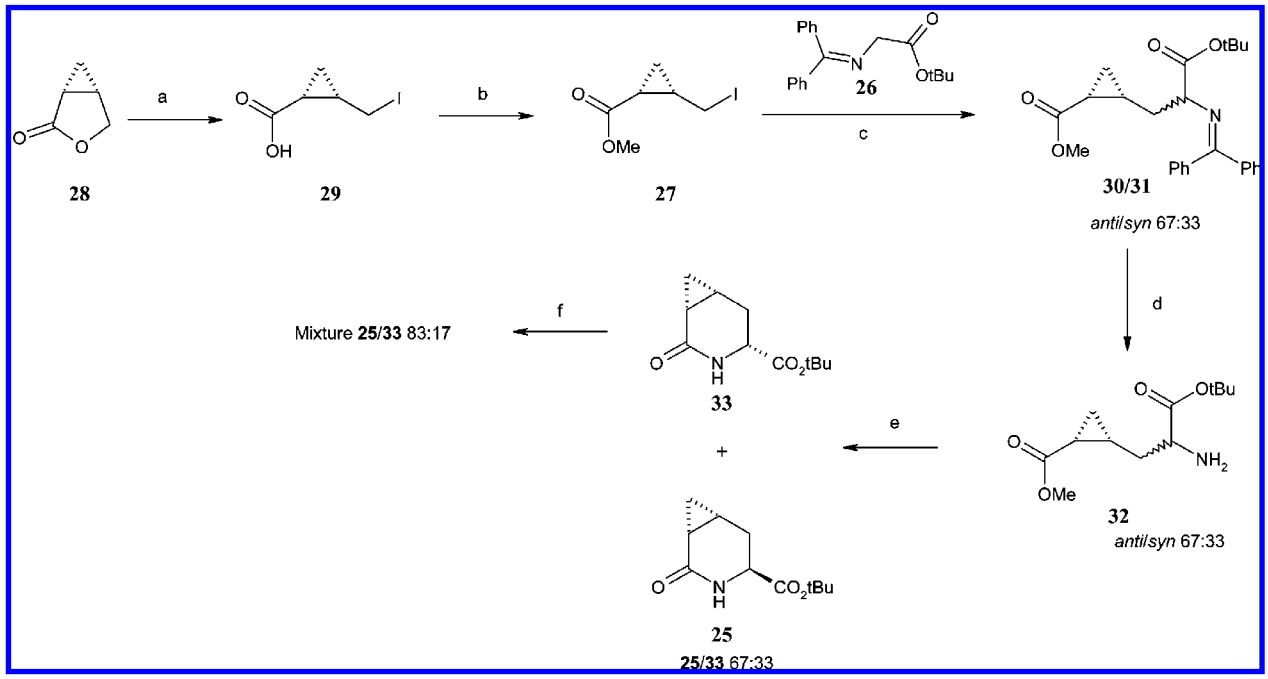
Therefore, a more efficient scalable synthesis for **4** was necessary.

Chemical Development Synthesis. Considering the difficulty to form the cyclopropyl moiety, we sought to focus our retrosynthetic approach on a chiral cyclopropyl starting material. Therefore, a new scalable route was identified, which involved an alkylation of glycine derivative **26** with alkyl iodide **27** obtained in two steps from commercially available chiral lactone[8] **28** as depicted in Scheme 5.

The synthesis started from the opening of chiral lactone **28** (>99% ee) with TMSI,[9] generated in situ using trimethylsilylchloride (TMSCl) and sodium iodide in acetonitrile at 50 °C

(8) Chiral lactone **28** can be purchased from Minakem or Dr. Reddys. For the syntheses of **28** see: (a) Sabbioni, G.; Jones, J. B. *J. Org. Chem.* **1987**, *52*, 4565–4570. (b) Bolm, C.; Schiffers, I.; Dinter, C. L.; Gerlach, A. *J. Org. Chem.* **2000**, *65*, 6984–6991. (c) Peschiulli, A.; Gun'ko, Y.; Connon, S. J. *J. Org. Chem.* **2008**, *73*, 2454–2457. (d) Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763–5775.

Scheme 6. **Chemical development synthesis**[a]



[a] Reagents and conditions: a) TMSCl, NaI, CH_3CN; b) TMSCl, MeOH; c) KOtBu, 2-MeTHF, 0 °C; d) 30% w/w citric acid; e) i. HCl cat., toluene, reflux; ii. *n*-heptane; f) DBU, toluene, reflux (60% overall yield).

(Scheme 6). Under these conditions the reaction is fast and clean. Some attempts to precipitate **29** were conducted involving solubility screening. In the best precipitation conditions (addition of water to the reaction mixture), the isolated yield was only 70% (25% of the product was still present in the mother liquor). Instead of isolating **29**, a solvent swap with methanol was done. The next step, methyl ester formation, was carried out under classical conditions using trimethylsilylchloride in methanol at room temperature. The reaction performed well and provided product in high yield. Unfortunately, the methyl ester **27** is an oil, and therefore, direct isolation was not ideal. A procedure was developed whereby **27** was isolated as a solution suitable for the next reaction. This work-up included methanol displacement *via* distillation with 2-methyltetrahydrofuran (2-MeTHF), aqueous reductive work-up to destroy any trace of iodine, and extractive work-up and distillation to azeotropically dry the 2-MeTHF solution. The solution of **27** in 2-MeTHF was then used in the next transformation.

Conversion of **27** to the lactam **25** was achieved using a three-step procedure. Addition of **27** to the preformed anion of *N*-(diphenylmethylene)glycine *tert*-butyl ester **26** using potassium *tert*-butoxide at 0 °C provided a diastereoisomeric mixture of **30** and **31** in a good yield.[10] The diastereoisomeric ratio at this point was 67:33 in favor of the desired *anti* isomer **30** (precursor of the desired lactam **25**). As **30** and **31** were oils and therefore column chromatography was necessary to separate them, we sought to postpone the isolation and purification until later on in the synthesis, as it is known that compounds **25** and **33** are solids.

Knowing that the benzophenone imine deprotection conditions used aqueous citric acid[11] and the cyclization step was accomplished at reflux in toluene, a telescoping procedure was investigated. After nucleophilic substitution of the iodide **27**, the mixture was treated with aqueous citric acid solution to afford a solution of the diastereoisomeric aminoacids **32** and benzophenone. The resulting acidic aqueous solution was then washed with cyclohexane to remove the benzophenone and then the aqueous layer was basified. The free amine **32** could be extracted with ethyl acetate which was then displaced *via* distillation by toluene, in order to have a higher boiling point solvent. The solution of **32** in toluene was refluxed to induce thermal cyclization to furnish the lactames **25** and **33**. Then the mixture was cooled to room temperature which induced partial precipitation of **33**. Nevertheless, the process was not robust enough since the reaction time during the last step (lactam formation) was not reproducible (from 12 h to 4 days during the first kilo laboratory experiments). To solve this issue, a catalytic amount of 37% aqueous hydrochloric acid was added and provided a consistent reaction time of 23 h. Unfortunately, the same diastereoisomeric ratio present in the mixture **30**/**31** is observed also in the mixture **25**/**33**.

As the diastereoselectivity of the coupling reaction between **27** and **26** is moderate, a decrease of the reaction temperature to improve the selectivity was investigated. Nevertheless, only the reaction rate (slower reaction) was affected and not the diastereoisomeric ratio. Although asymmetric additions to *N*-(diphenylmethylene)glycine *tert*-butyl ester using Maruoka's catalyst[12] were planned, time restrictions limited exploration of

(9) Kolb, M.; Barth, J. *Synth. Commun.* **1981**, *11*, 763–767.
(10) Kozhushkov, S. I.; Zlatopolskiy, B. D.; Brandl, M.; Alvermann, P.; Radzom, M.; Geers, B.; de Meijere, A.; Zeeck, A. *Eur. J. Org. Chem.* **2005**, 854–863.
(11) (a) O'Donnell, M. J.; Boniece, J. M.; Earp, S. E. *Tetrahedron Lett.* **1978**, *19*, 2641–2644. (b) Yamada, S. I.; Oguri, T.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1976**, 136–137.

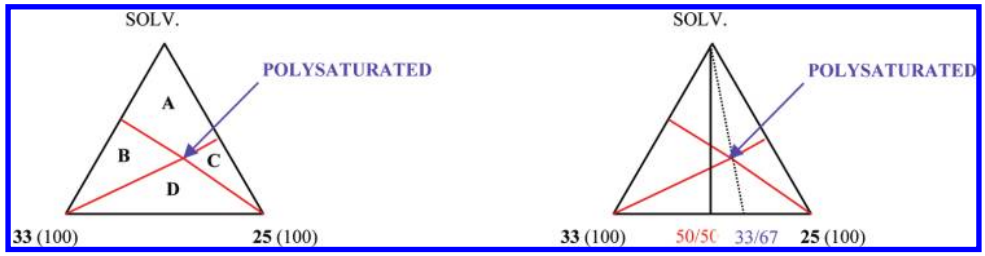


Figure 1. **Phase diagram for compounds 25 and 33.**

such alternatives to future research. As a result, different approaches were applied in order to isolate the pure *anti* isomer **25**:

1 chromatographic separation
2 selective crystallization
3 epimerization of *syn* diastereoisomer **33**

As the first approach was the least desirable, most of the efforts were concentrated on the second and third solution in view of future scale-ups, where chromatography is not practical, time-consuming, and environmentally unfriendly.

The direct crystallization is one of the most popular methods to enrich the diastereoisomeric purity of a compound, and with one simple experiment it is possible to understand if this approach is feasible: building the ternary phase diagram and determining the polysaturated solution as depicted in Figure 1.[13]

In the phase diagram, four zones are identified: zone A, where both diastereoisomers **25**/**33** are in solution; zone B, where **33** crystallizes out leaving mainly **25** in solution; zone C, where **25** crystallizes out leaving mainly **33** in solution; and finally zone D, where both diastereoisomers **25**/**33** crystallize. In our case, the polysaturated point was determined by suspending a mixture of **25**/**33** in toluene and leaving the mixture to reach the equilibrium. Analysis of the mother liquors showed a **25**/**33** ratio of 67:33. As shown in Figure 1 (right-hand side diagram), in principle it is possible to dissolve a mixture **25**/**33** in a ratio 50:50 and precipitate the pure isomer **33**, leaving the mother liquors enriched in compound **25** by using an amount of solvents that allows crystallization and isolation of the product within zone B.

Unfortunately, as we wanted to isolate the isomer **25**, this approach was not useful for our objective. In addition, because the reaction between **27** and **26** afforded a mixture of **30**/**31** (and subsequently a mixture **25**/**33**) in the same ratio of the polysaturated solution, a crystallization would deliver a solid once again with a 67:33 ratio, and therefore none of the two compounds could be selectively precipitated. The same exercise was applied to a mixture of the corresponding acids **34**/**35**.[14]

Upon suspending a mixture of acids **34**/**35** in a ratio 72:28 in dichloromethane, it was found that the composition of the polysaturated solution was *anti*/*syn* 59:41, so that in principle it was possible to partially precipitate the desired diastereoisomer **34** (Figure 2). The main issues were that the crystallization had to be run in a large volume of dichloromethane (clearly this could have been solved by searching for a solvent where **35** was more soluble) and that, because we started from a 67:33 mixture, the maximum possible recovery of pure *anti* isomer was calculated to be 20%. On the basis of these scarce results, this approach was discarded.

In parallel, an important breakthrough was obtained following the third approach, i.e. the epimerization of the undesired diastereoisomer **33**. Indeed, the undesired diastereoisomer **33** in the presence of DBU in toluene afforded a mixture in a 83:17 ratio in favor of **25**.

Having shown the possibility to epimerize the undesired diastereoisomer under basic conditions in favor of the desired one, it was decided to isolate both esters **25**/**33** from the reaction mixture after lactam formation, and then isomerize the undesired diastereoisomer. Indeed, the addition of *n*-heptane as antisolvent led to the precipitation of **25**/**33** in an excellent quality. Thus, the telescoped procedure for the chiral lactone opening, esterification, alkylation reaction of **26** with **27**, hydrolysis, cyclization, and isolation produced 1.6 kg of **25**/**33**[15] in high purity for an overall yield of 60% over five steps.

With a robust procedure to synthesize the lactam as an *anti*/*syn* mixture in 67:33 ratio, the next transformation entailed an appropriate epimerization of this intermediate to then reach efficiently the key scaffold, **4**.

Since DBU in toluene was able to epimerize the undesired diastereoisomer **33** and provided an 83:17 ratio in favor of **25**, a screening of 14 additional solvents was performed to improve this ratio. Unfortunately, no improvement was obtained.

Nevertheless, from an extended base screening, it emerged that, treating a mixture **25**/**33** in 67:33 ratio with powdered potassium hydroxide in 2-propanol/toluene at reflux, epimer-

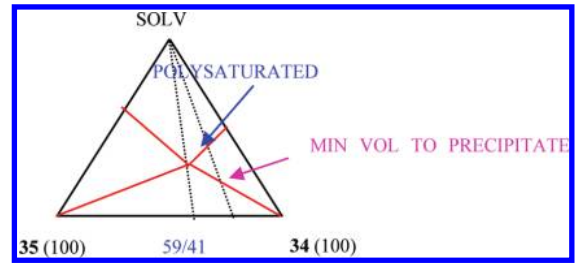
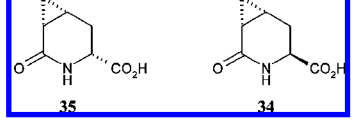
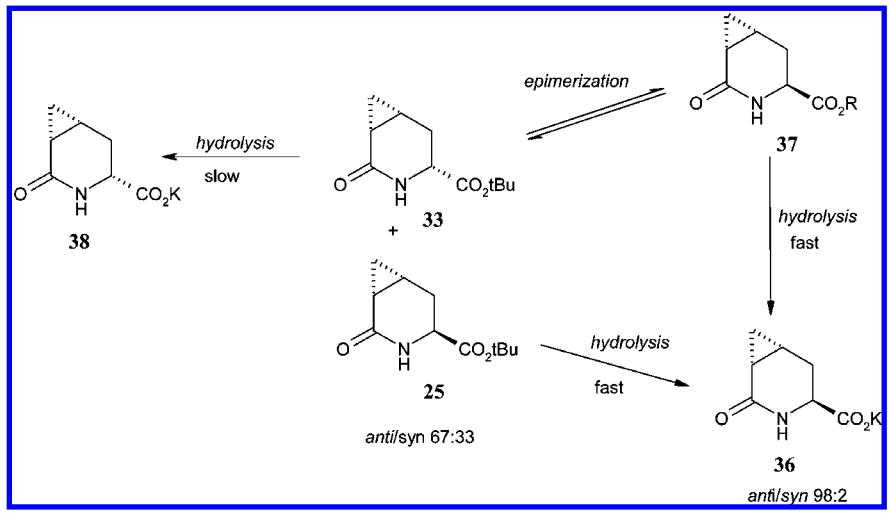


Figure 2. **Phase diagram for compounds 34 and 35.**

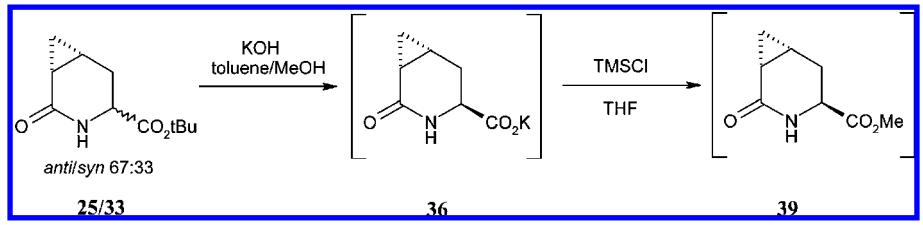
(12) (a) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656–5682. (b) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013–3028.
(13) Marchand, P.; Lefèbvre, L.; Querniard, F.; Cardinaël, P.; Perez, G.; Counioux, J.-J.; Coquerel, G. *Tetrahedron: Asymmetry* **2004**, *15*, 2455–2465.
(14) A 72:28 mixture of *tert*-butyl ester **25**/**33** resulting from column chromatography and treated with trifluoroacetic acid afforded quantitatively the corresponding carboxylic acid **34**/**35** in a 72:28 ratio.



Scheme 7. **Hypothetical epimerization mechanism**



Scheme 8



ization/ester hydrolysis occurred, giving a ratio of 98:2[16] in favor of the *anti* diastereoisomer of the corresponding potassium salt (**36**, Scheme 7). This result could be explained because the hydrolysis of the *syn* ester is slower than its epimerization to the *anti* ester, as depicted in Scheme 7. Although the reaction was very clean and the diastereoisomeric ratio was high (96% de), the isolation of the salt was not feasible because of its high hygroscopicity.

We decided to convert the carboxylic acid salt **36** into the corresponding methyl ester, speculating that the methyl ester might be isolated as a solid. Therefore, a solvent screening was performed in order to develop a two-step, one-pot procedure. Thus, addition of powdered potassium hydroxide to a solution of **25**/**33** in toluene/methanol, then followed by addition of an excess of TMSCl led to the complete conversion to **39** (Scheme 8). The remarkable success of these reactions provided us with a simple and efficient procedure to recycle the undesired diastereoisomer **33** into the desired one. Unfortunately, the methyl ester **39** is very soluble in water, prohibiting any possible aqueous work-up to remove any inorganic impurity. Thus, an adequate work-up was optimized to obtain **39** as solution suitable for use in the next reaction. After complete conversion to the methyl ester, methanol and toluene were partially displaced *via* distillation with THF, which was the desired solvent for the subsequent transformation.

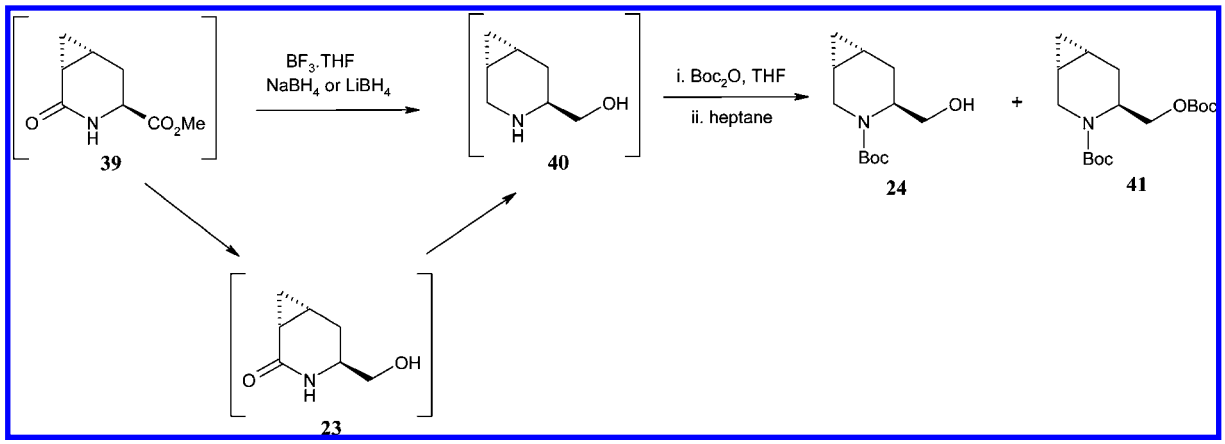
Indeed, the next step required the complete reduction of **39** to produce the desired aminoalcohol **40**, followed by the protection of the resulting secondary amine to afford the desired scaffold **4**. Originally, this two-step procedure was already performed by the medicinal chemists on a similar substrate. This reduction involved the use of BH_3 at reflux to reduce the lactam moiety, followed by protecting the secondary amine with *tert*-butoxycarbonyl group.

In process development for safety reasons, BH_3 is commonly replaced by the procedure generating BH_3 in situ by addition of BF_3·THF to sodium borohydride. However, addition of BF_3·THF to the mixture of **39** and sodium borohydride in THF did not give complete conversion and surprisingly led to a mixture of **23** and **40** in favor of **23** (Scheme 9). Investigation on lab scale showed that the premixing of **39** with BF_3·THF was required to have complete reduction. Consequently, the solution of **39** precomplexed with BF_3·THF was added to a suspension of sodium borohydride at 30 °C affording **40**.

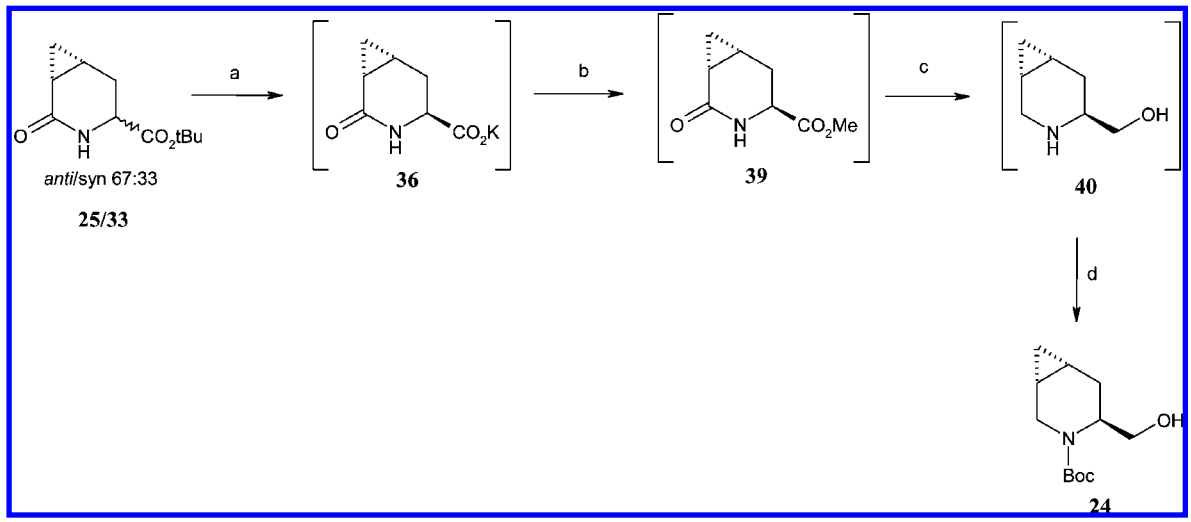
However, the conversion was not reproducible when we scaled up. We reasoned that the difficulty to reach complete conversion stemmed from the heterogeneous aspect of the reaction mixture. To overcome this, we replaced powdered sodium borohydride by a solution of lithium borohydride in THF as reducing agent. Thus, the reaction was cleaner, faster, and was not scale dependent. Because of the high water solubility of **40**, the work-up was optimized, isolating **40** as a suitable solution for the use in the next reaction. The procedure included careful quench of the excess of borane with methanol at 50 °C, distillation to remove methanol and the boronic ester, 6 M aqueous hydrochloric acid treatment to destroy amino boronate complex and finally careful basification of aqueous layer. The basic aqueous solution of **40** in THF in the presence of a slight excess of Boc-anhydride afforded **24**, which can be precipitated by addition of *n*-heptane in moderate yield (Scheme 9). In fact, the presence of a large amount of two impurities (4-chlorobutanol and *n*-butanol) resulting from the THF deg-

(15) The analytical standards of **25** and **33** were obtained by column chromatography separation on silica gel (eluent: cyclohexane/ethyl acetate 7:3).
(16) Ratio obtained in solution.

Scheme 9



Scheme 10[a]



[a] Reagents and conditions: a) KOH, toluene/MeOH; b) i. TMSCl; ii. $NaHCO_3$, THF; c) $LiBH_4$ (4 M in THF), BF_3·THF; d) i. Boc_2O, THF; ii. isooctane (73% overall yield).

radation were able to solubilize **24** and therefore decrease the overall yield. Additionally, **24** was contaminated by **41**, the result of a double protection during the last step (Scheme 9).

To increase the recovery of **24**, several modifications of the reaction conditions were introduced. First, the decrease of the amount of Boc-anhydride to 0.98 equiv and a pH control (pH = 9) of the reaction mixture were able to prevent the formation of **41** and to obtain a very clean reaction profile. Second, 4-chlorobutanol was found to derive during the solvent swap from methanol to THF after the formation of the methyl ester due to the presence of hydrogen chloride (arising from TMSCl and MeOH) and also from the 6 M HCl treatment of the amino boronate complex initially done at reflux. Consequently, to prevent its formation, after the formation of the methyl ester **39**, the reaction mixture was neutralized with powdered $NaHCO_3$ prior to solvent swap, while the cleavage of the amino boronate complex was performed at room temperature. Regarding the removal of *n*-butanol (due to the THF opening by lithium borohydride), it was achieved by washing the acidic aqueous layer with toluene prior to basification and Boc-protection. Finally, an extensive solubility screening was performed to identify the best precipitation conditions. Among the solvents screened, isooctane proved to be the most suitable solvent for the isolation.

Thus, these modifications were implemented, and the five telescoped-step procedure involving epimerization/hydrolysis, methyl esterification, concomitant reduction of both lactams to amine and ester to alcohol, protection and isolation gave over four batches, 3 kg of **24** in high purity (98% by HPLC, >99% ee and >99% de) and in an overall yield of 73% (Scheme 10).

It is worth noting that most of the intermediates were not UV sensitive; therefore, the reaction monitoring was a real challenge. Analytical procedures were developed to monitor the reaction *via* proton NMR.

In conclusion, an efficient and scalable synthetic route for the synthesis of the key related scaffold **24**, a common intermediate required for the synthesis of the targeted molecules **1**, has been developed from the commercially available chiral lactone **28**. One of the key steps is the epimerization of the undesired diastereoisomer **33**. Compared to the discovery route and Medicinal Chemistry Support synthesis, this route offers significant advantages in terms of yield (44% overall versus 24% for Medicinal Chemistry and 6% for Medicinal Chemistry Support) with only two isolations *via* precipitation and avoiding

all chromatography purifications. This process has been utilized on kilo lab scale to produce over 3 kg of **24**.

Experimental Section

All the materials were purchased from commercial suppliers and used without further purification. All reactions were carried out under atmosphere of nitrogen.

1,1-Dimethylethyl-(1*R*,4*S*,6*R*)-2-oxo-3-azabicyclo[4.1.0]heptane-4-carboxylate (25) and 1,1-Dimethylethyl-(1*R*,4*R*,6*R*)-2-oxo-3-azabicyclo[4.1.0]heptane-4-carboxylate (33). Sodium iodide (2.76 kg, 18.4 mol, 1.5 equiv) was partially dissolved in acetonitrile (12 L) after stirring at 20 °C for 10 min under nitrogen atmosphere. TMSCl (2.3 L, 18.4 mol, 1.5 equiv) was added over 15 min, and the resulting yellow slurry was stirred at 20 °C for 1 h. A solution of (1*R*,5*S*)-3-oxabicyclo[3.1.0]hexan-2-one (**28**, 1.2 kg, 12.2 mol, 1 equiv, > 99% ee, $[\alpha]^D = +61.5°$ (c = 1, $CHCl_3$)) in acetonitrile (2.4 L) was added over 5 min at 20 °C. The suspension was heated to 50 °C (internal temperature) and then kept for 2 h at 50 °C. The mixture was diluted with methanol (12 L) at 20 °C and concentrated to 5 volumes (6 L) under reduced pressure. Methanol (12 L) was then added followed by TMSCl (0.72 L, 5.7 mol, 0.5 equiv). The resulting mixture was stirred at 20 °C overnight. The mixture was concentrated under vacuum to 5 volumes (6 L), then 2-MeTHF was added (12 L), and the solution was concentrated to 5 volumes (6 L). 2-MeTHF was added (12 L). The dark-red solution was washed with aqueous 20% w/w Na_2SO_3 (4.8 L) at 20 °C (solution became colourless−light yellow). The biphasic system was separated, and the organic layer was washed with water (4.8 L), then concentrated under vacuum to 4 volumes (4.8 L). 2-MeTHF (12 L) was added, and the solution was concentrated to 5 volumes (6 L), to obtain finally the solution of methyl (1*R*,2*S*)-2-(iodomethyl)cyclopropanecarboxylate **27**.

N-(Diphenylmethylene)glycine *tert*-butylester (**26**, 3.6 kg, 12.2 mol, 1 equiv) was suspended in dry 2-MeTHF (12 L) at 20 °C. The mixture was cooled to 0 °C, and KO*t*Bu (1.38 kg, 12.3 mol, 1 equiv) was added in three portions. The slurry became a yellow-orange solution and was stirred at 0 °C for 30 min. The previous solution of methyl-(1*R*,2*S*)-2-(iodomethyl)cyclopropanecarboxylate **27** in 2-MeTHF was slowly added over 25 min, keeping the temperature lower than 5 °C during the addition. The mixture was stirred at 0 °C for 2.5 h. The mixture was quenched with buffer pH = 7 (KH_2PO_4/Na_2HPO_4, 2.4 L) at 0 °C. The biphasic system was warmed at 20 °C. The water phase was discharged. The organic phase was cooled to 0 °C and treated with 30% w/w citric acid (9.6 L). The biphasic system was warmed to 20 °C and stirred overnight at 20 °C. Cyclohexane (24 L) was added, and the phases were separated. The water phase was washed with cyclohexane (24 L). Ethyl acetate (24 L) was added to the aqueous phase, and then the system was basified to pH = 8.5 with aqueous saturated K_2CO_3 (6 L) and then diluted with water (3 L). The biphasic system was separated. The aqueous layer was back extracted with ethyl acetate (24 L). The combined organic phases were washed with water (3.6 L) and concentrated to 10 volumes (12 L). Toluene (24 L) was added, and the solution was concentrated to 10 volumes (12 L) and diluted again with toluene (4.8 L). To this solution was added 37% aqueous HCl (6 mL, catalytic amount). The solution was heated to 105 °C for 23 h. The solution was cooled at 40 °C and reduced to 4 volumes (4.8 L) under reduced pressure, and *n*-heptane (8.4 L) was added over 1 h. The mixture was stirred at 40 °C for 30 min and then cooled at 15 °C over 1 h; a solid was precipitated. The slurry was stirred at 15 °C for approximately 16 h and then filtered. The solid was washed with *n*-heptane (2 × 3 L) and dried in a vacuum oven at 40 °C. 1,1-Dimethylethyl-(1*R*,4*S*,6*R*)-2-oxo-3-azabicyclo[4.1.0]-heptane-4-carboxylate (**25**) and 1,1-dimethylethyl-(1*R*,4*R*,6*R*)-2-oxo-3-azabicyclo[4.1.0]heptane-4-carboxylate (**33**) (1.58 kg, 60%) were obtained as white solids in 67:33 ratio.

(**25**) ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 6.86 (br s, 1H), 3.75 (dd, J = 11.9, 4.7 Hz, 1H), 2.20 (ddd, J = 13.2, 4.5, 2.3 Hz, 1H), 1.74 (td, J = 12.6, 3.4 Hz, 1H), 1.42 (s, 9H), 1.40−1.60 (m, 2H), 1.12 (q, J = 5.3 Hz, 1H), 0.90 (ddd, J = 9.3, 7.9, 5.3 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 7.0, 12.5, 15.6, 24.6, 27.5, 49.7, 81.4, 170.1, 171.0. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{11}H_{17}NO_3$: 212.1287; found 212.1288.

(**33**) ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.39 (d, J = 4.9 Hz, 1H), 3.87 (dddd, J = 8.2, 5.2, 1.3, 0.7 Hz, 1H), 2.33 (d, J = 13.9 Hz, 1H), 2.11 (ddd, J = 14.2, 8.1, 3.2 Hz, 1H), 1.42 (s, 9H), 1.35−1.60 (m, 2H), 0.87 (m, 1H), 0.69 (td, J = 5.4, 4.4 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 9.0, 13.9, 15.6, 21.8, 27.5, 51.2, 81.1, 170.8, 172.7. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{11}H_{17}NO_3$: 212.1287; found 212.1288.

1,1-Dimethylethyl-(1*R*,4*S*,6*R*)-4-(hydroxymethyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate (24). The mixture of 1,1-dimethylethyl (1*R*,4*S*,6*R*)-2-oxo-3-azabicyclo[4.1.0]heptane-4-carboxylate (**25**) and 1,1-dimethylethyl-(1*R*,4*R*,6*R*)-2-oxo-3-azabicyclo[4.1.0]heptane-4-carboxylate (**33**) (1 kg, 4.73 mol, 1 equiv) as 67:33 ratio was dissolved in toluene (3 L) and MeOH (7 L) and stirred for 5 min at 20 °C. The mixture was cooled to 15 °C, and powdered KOH (0.4 kg, 7.13 mol, 1.5 equiv) was added in eight portions over 1 h. The solution was stirred at 20 °C for 3 h. The solution was cooled to 10 °C, and TMSCl (2.4 L, 18.9 mol, 4 equiv) was added, keeping the temperature around 10−15 °C over 45 min. White solid was precipitated (KCl). The slurry was stirred at room temperature overnight. $NaHCO_3$ solid (1.4 kg) was added in three portions to reach pH = 5. The mixture was concentrated to 4 volumes (4 L). THF (8 L) was added, and the volume was reduced to 4 volumes (4 L) by distillation under reduced pressure. The solid was filtered and washed with THF (3 × 2 L). The filtrate appeared cloudy. The solution was reduced to 2.5 volumes (2.5 L) by distillation under reduced pressure, and BF_3·THF (3.13 L, 28.4 mol, 6 equiv) was added under stirring whilst maintaining an internal temperature of 25 °C. The resulting solution was added slowly to a solution of $LiBH_4$ (4 M in THF, 4.8 L, 19.2 mol, 4 equiv), diluted with THF (3 L), keeping the temperature at 25−30 °C [the line was washed with THF (0.5 L)]. The mixture was stirred at 30 °C overnight (17 h). The mixture was slowly quenched with MeOH (4 L) at 25−30 °C (addition time in about 1 h). The solution was stirred at 50 °C for approximately 1 h. After this time, the solution was reduced to 5.5 volumes (5.5 L) by distillation under reduced pressure.

HCl [3 M (4 L)] was then added at 10−15 °C. The mixture was stirred at 20 °C for 1 h and toluene (4 L) was added. The phases were separated. The aqueous phase was washed with toluene (3 × 4 L). The aqueous layer was basified with 6 M NaOH (3.5 L) until pH = 9. To the basic aqueous solution at 25 °C were successively added THF (0.5 L) and a solution of di-*tert*-butyl dicarbonate (1 kg, 4.58 mol, 0.98 equiv) in THF (1 L). The pH was adjusted to 9 by addition of 6 M NaOH (1.2 L). The resulting slurry was stirred for 30 min at 25 °C, and the pH was adjusted to pH = 9 by addition of 6 M NaOH (1 L). The slurry was then stirred for 3 h and then filtered. The inorganic salts were washed with TBME (2 × 2 L). The filtrate was diluted with TBME (2 L). The biphasic system was separated. The aqueous layer was back extracted with TBME (6 L), and the combined organic phases were washed with NaCl 20% w/w (4 L) and then concentrated under reduced pressure to 5 volumes (5 L). Isooctane (10 L) was added and the solution was reduced to 6 volumes (6 L) by distillation under reduced pressure. Seed (1 g) of the title compound was added at 40 °C, and the slurry was cooled at 20 °C in 30 min to allow precipitation. The slurry was stirred for at least 4 h and filtered. The solid was washed with cold isooctane (2 × 2 L) and dried in a vacuum oven at 40 °C. 1,1-Dimethylethyl-(1*R*,4*S*,6*R*)-4-(hydroxymethyl)-3-azabicyclo[4.1.0]heptane-3-carboxylate (**24**, 0.8 kg, 73%) was obtained as white solid (98% purity by HPLC). Chiral HPLC analysis of **24** showed product with >99% ee and no trace of undesired *syn* diastereoisomer. Mp = 71 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 4.66 (br m, 1H), 3.65−3.85 (br m, 2H), 3.41 (br m, 1H), 3.37 (m, 1H), 3.20−3.35 (br m, 1H), 1.89 (m, 1H), 1.53 (ddd, J = 14.3, 6.8, 3.3 Hz, 1H), 1.37 (s, 9H), 0.91 (m, 2H), 0.58 (br m, 1H), −0.09 (q, J = 4.8 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ (ppm) 5.2, 8.4/8.5, 8.8/8.9, 22.3/22.8, 28.1, 37.2/38.2, 49.2/50.4, 60.8/61.2, 78.3/78.4, 154.7/154.9. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{12}H_{21}NO_3$: 228.1600; found 228.1608.

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