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Synthesis of All Four Stereoisomers of 3-(*tert*-Butoxycarbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic Acid

Bettina Bakonyi,[†] Markus Furegati,*[,‡] Christian Kramer,[§] Luigi La Vecchia,[‡] and Flavio Ossola[‡]

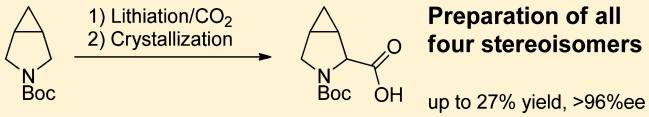
[†]Doetsch Grether AG, Falkensteinerstrasse 37, 4132 Muttenz, Switzerland

[‡]Preparations Laboratories, Global Discovery Chemistry, Novartis Institutes for Biomedical Research, Klybeckstrasse 141, 4057 Basel, Switzerland

[§]Institute of General, Inorganic and Theoretical Chemistry and Center for Molecular Biosciences Innsbruck (CMBI), University of Innsbruck, Innsbruck, Austria

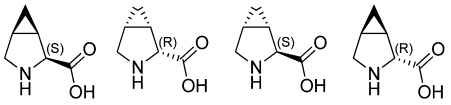
Supporting Information

ABSTRACT: A synthesis of all four stereoisomers of 3-(*tert*-butoxycarbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid has been developed, thereby significantly shortening the known literature procedures for the syntheses of these unnatural amino acids. With a simple adjustment of the reaction conditions, we were able to obtain either pure *cis* or *trans* acid. Optical resolution was accomplished via diastereomeric salt formation or alternatively via chromatography on a chiral stationary phase. Finally, *ab initio* calculations gave an explanation for the observed *cis* selectivity in the initial step.



INTRODUCTION

The four stereoisomers of 3-azabicyclo[3.1.0]hexane-2-carboxylic acid (series **1**), also referred to as 2-carboxy-3,4-methanopyrrolidines or 3,4-methanoprolines, belong to a unique class of amino acids.[1] The naturally occurring nonproteinogenic amino acid (*S*)-*cis*-**1** derived from L-proline was discovered in 1969 in the fresh seeds of the American horse chestnut, *Aesculus parviflora*,[2] and also found in the stem tissue of *E. foeminea*.[3]



In the first three decades after the discovery of the 3-azabicyclo[3.1.0]hexane-2-carboxylic acids only little has been published about this compound class. In 1980, the racemic mixture of both geometric isomeric forms was found to be active as plant male gametocides.[4] It has also been shown that (*S*)-*cis*-**1** and (*S*)-*trans*-**1** strongly inhibit the proline permease in *E. coli*.[5] (*S*)-*trans*-**1** (referred to as exo) has been marketed by Calbiochem AG as a male sterilant in wheat.[6] Since 2004, all four stereoisomers have been patented for a range of applications.[7]

Shortly after the first isolation of (*S*)-*cis*-**1**, a chemical synthesis was published (Scheme 1A). The synthesis begins with protection of functional groups of (*S*)-2,5-dihydro-1*H*-pyrrole-2-carboxylic acid (**2**). *N*-Trifluoroacetyl-3,4-dehydro-L-proline methyl ester (**3**) was then treated, neat, with copper(I) chloride and excess diazomethane to give the cyclopropyl amino acids (*S*)-*cis*-**1** and (*S*)-*trans*-**1** in a *cis* to *trans* ratio of 1:3.5 after deprotection.[2b] A second synthesis (Scheme 1B), starting from 3-azabicyclo[3.1.0]hexane (**4**), involves addition of a carboxy group in position 2, introduced via chlorination of the nitrogen, elimination of HCl to the imine, formation of the bisulfite adduct, and treatment with sodium cyanide followed by saponification with barium hydroxide (Scheme 1B).[8] The racemic mixture of *cis*- and *trans*-2-cyano-3-azabicyclo[3.1.0]-hexanes (**5**) was separated and converted to the corresponding acid mixture **6**.[9] The *cis*/*trans* mixture **5** has been also prepared by cyclizing *cis*-1-ethoxycarbonyl-2-formylcyclopropane (**7**) with ammonia and hydrogen cyanide followed by the reduction of the intermediate 2-cyano-3-azabicyclo[3.1.0]hexane-4-one (**8**) (Scheme 1C).[10] Conversion of *cis*-ethyl-2-cyanocyclopropylcarboxylate (**9**) to *cis*-2-aminomethyl-cyclopropyl-1,2-diethylacetal (**10**) and ring closure to the pyrrolidine ring gave racemic (*S*)-*cis*-**1** in eight steps (Scheme 1D).[4] Alternatively, *rac*-*cis*-**1** was prepared via ring contraction of 5-chloro-3-azabicyclo[4.1.0]heptane-4-one (**12**), which was prepared from 3-hydroxyimino[3.1.0]hexane (**11**) in three steps (Scheme 1E).[11]

Starting with the chiral synthons **13** and (*R*)-glycidyl triflate (**14**), (*S*)-*cis*-**1** was obtained in six linear steps in 34% overall yield (Scheme 2F) via intermediate **15**.[12] (*S*)-*cis*-**1** was also prepared in a 10-step sequence containing a formal insertion of the cyclopropylidene (derived from **17**) or a related carbenoid into the C−H bond adjacent to nitrogen as the key step to form bicyclo system **18** (Scheme 2G). The overall yield was 40%; however, starting material **16** first had to be prepared via oxidation of 1,1-dibromo-2-vinylcyclopropane with $KMnO_4$ followed by resolution with dehydroabietylamine.[13] The HCl salt of (*S*)-*trans*-**1** was prepared in 11 steps (11% overall yield)

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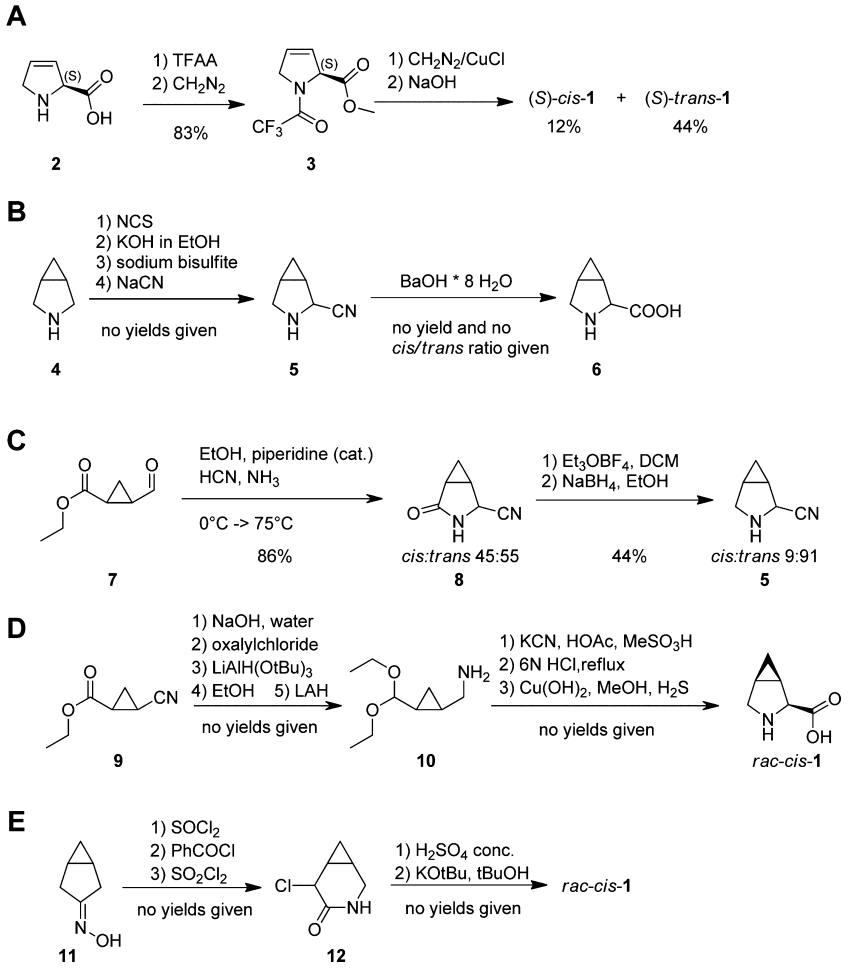
Scheme 1. Syntheses A–E of 3-Azabicyclo[3.1.0]hexane-2-carboxylic Acid



starting from L-pyroglutamic acid (**19**) (Scheme 2H). The rigid structure of the *O*,*N*-acetal **20** with the directing phenyl ring allowed the stereoselective cyclopropanation to **21**.[14] A more recent route toward (*S*)-*trans*-**1** also started from L-pyroglutamic acid (**19**) (Scheme 2I). Protection of the carboxylic acid as the ortho-ester **22** avoided reduction/oxidation steps. The double bond in **22** was introduced by a PhSeCl substitution/oxidation/elimination sequence. A 1,3-dipolar cycloaddition with diazomethane followed by a photoinduced ring contraction forming **23** were the key steps. (*S*)-*trans*-**1** was obtained in an overall yield of 10% in 12 linear steps. (*S*)-*cis*-**1** was prepared in 15 steps via the same intermediate **22** respectively.[15] All the above-described syntheses are rather lengthy, and not all starting materials are easily accessible. From a user's standpoint, a short synthesis allowing access to all four stereoisomers is desirable.

RESULTS AND DISCUSSION

In this contribution we would like to present two approaches to prepare enantiopure *cis* and *trans* 3-(*tert*-butoxycarbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acids, (*R*)/(*S*)-*cis*- and (*R*)/(*S*)-*trans*-**30**. We started our investigations with *tert*-butyl 3-azabicyclo[3.1.0]hexane-3-carboxylate (**24**), as it became commercially available in kilogram quantities or can be prepared in five steps from commercial cyclopropyl-1,2-dicarboxylic acid (Scheme 3).[16] After lithiation and quenching with CO_2 gas we obtained *cis*-3-(*tert*-butoxycarbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (*rac*-*cis*-**30**) with a stereospecificity greater than 99%.

Lithiation of Prolines and the Use of Diamine Additives. Barker et al. showed that the diamine-free lithiation of *tert*-butyl pyrrolidine-1-carboxylate (1.3 equiv of *sec*-BuLi in THF for 1 h at −40 °C) and subsequent reaction with benzaldehyde gave 64% of the addition product.[17] In our hands, when these conditions were translated to the lithiation of substrate **24** followed by quenching with CO_2, neither the *cis*- nor the *trans*-acid was observed (Scheme 3 and Table 1 entry 1).[18]

A mixture of *sec*-BuLi/TMEDA is widely used in lithiation reactions. For example, the lithiation of *tert*-butyl pyrrolidine-1-carboxylate (Boc-pyrrolidine) followed by reaction with various electrophiles has been extensively described in the literature,[19] also with CO_2 as the electrophile.[20] The lithiation of our substrate **24** in diethyl ether at −70 °C and subsequent reaction with trimethylborate without elucidation of the stereochemical outcome has been also described.[16b,21] The presence of a stoichiometric amount of TMEDA accelerates and directs the deprotonation at low temperatures.[22] Other chelating diamines have been used for this purpose as well. For example 3,7-dipropyl-3,7-diazabicyclo[3.3.1]nonane (**27**) in the lithiation of *N*-*tert*-butyloxycarbonyl-3-azabicyclo[3.3.0]octane using *sec*-BuLi[23] allows the direct formation of mostly the *trans* product.[24] More literature about related carbanion electrophilic substitutions is given.[25]

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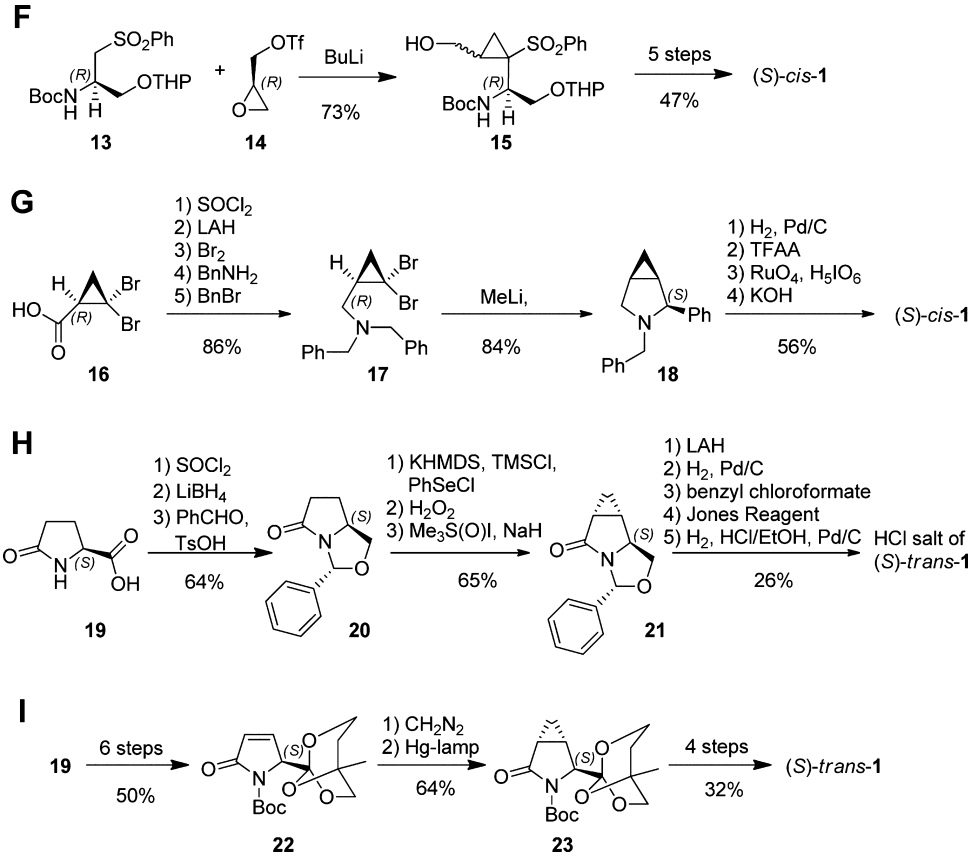
Scheme 2. Syntheses F–I of 3-Azabicyclo[3.1.0]hexane-2-carboxylic acid



Scheme 3. Literature Synthesis of 24: Lithiation/CO_2 Quenching and Benzylation Sequence

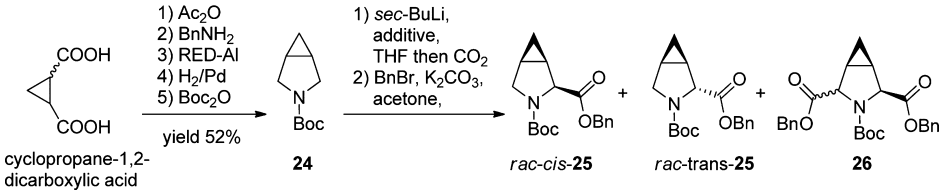
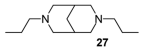


Table 1. Results of the Lithiation/CO_2 Quenching Step Depending on the Amine Additive

Entry	Additive	Reaction conditions	*rac-cis*-**25**	*rac-trans*-**25**	**26** [a]
1	none	5 h, –40°C	0	0	3
2	 **27**	5 h, –70°C	100 [b]	0	0
3	TMEDA	5 h, –70°C	77	2	21

[a]Structure suggestion based on MS data. [b]Area % HPLC at 215 nm. The numbers reflect the amounts of the different acids in the crude mixture after quenching with CO_2.

We performed two experiments in order to compare the efficiency of diamine **27** and the cheaper TMEDA. Our substrate **24** was lithiated with *sec*-BuLi/**27** or with *sec*-BuLi/TMEDA. The acids obtained were converted to the benzyl esters in order to facilitate analysis. With diamine **27** the isolated yield was 74% of pure *rac-cis*-**30** (Table 1 entry 2). The *trans* isomer was not observed. Using TMEDA the yield was 69%, but a mixture of *rac-cis*-**25**, *rac-trans*-**25**, and **26** was obtained (Table 1 entry 3). We therefore concluded that diamine **27** was required to give high diastereoselectivity for carboxylation and a maximum yield.

Enantioselective Deprotonation. Kerrick et al. showed that the deprotonation of *tert*-butyl pyrrolidine-1-carboxylate (**28**) with *sec*-BuLi/(−)-sparteine in Et_2O and subsequent quenching with CO_2 provided **29** in 55% yield with 88% ee.[26] The same conditions were applied to **24**, with the exception of a prolonged reaction time, resulting in only 32% yield and 73% ee of (*R*)-*cis*-**30** (Scheme 4). Due to this discouraging result, other sparteine-like chiral amines[27] were not tested. Rather

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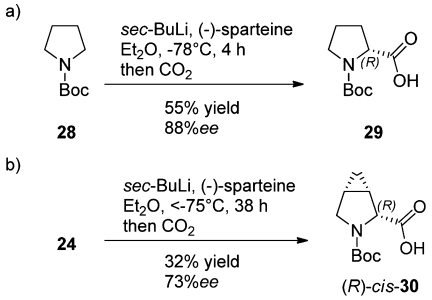
Scheme 4. Enantioselective Deprotonation: (a) Literature; (b) Own Work



than preparing the single enantiomers directly, we synthesized the racemic *cis*- and *trans*-Boc-protected 3-azabicyclo[3.1.0]-hexane-2-carboxylic acids (*rac-cis*-**30** and *rac-trans*-**30**) and resolved them using two alternative appoaches discussed below.

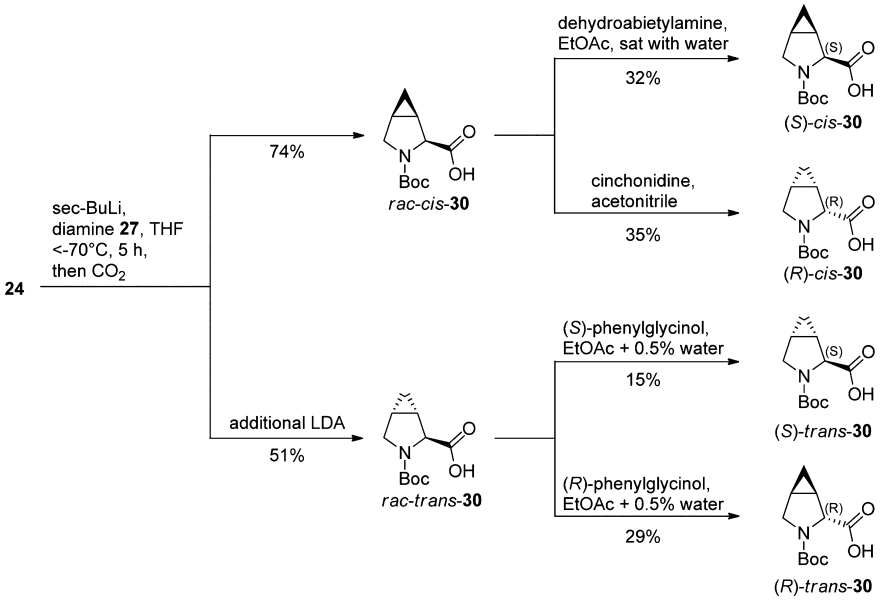
Approach 1: Resolution by Diastereomeric Salt Formation. Our first approach was to prepare *rac-cis*-**30** and *rac-trans*-**30** and resolve them via diastereomeric salt formation. The salt forming conditions were found by screening 192 different resolving agent and solvent combinations for both the *cis* and the *trans* acids (see Salt Screen in the Experimental Section for more details).

Synthesis of the *cis* Enantiomers. *rac-cis*-**30** was resolved with dehydroabietylamine into the (−)-enantiomer (*S*)-*cis*-**30** in 32% yield and with (−)-cinchonidine into the (+)-enantiomer (*R*)-*cis*-**30** in 35% yield (Scheme 5).

Synthesis of the *trans* Enantiomers. We found that it is possible to epimerize *rac-cis*-**30** to *rac-trans*-**30** via double deprotonation with LDA (*cis*/*trans* ratio of 1:9). We combined this epimerization step with the already established *rac-cis*-**30** synthesis (Scheme 5). Taking advantage of the fact that *rac-cis*-**30** existed as the mono-lithium salt in the reaction mixture, only one equivalent of LDA would be necessary to perform the epimerization. We observed, however, that excess CO_2 partially quenched the LDA[28] and prevented the reaction from reaching equilibrium. It was therefore necessary to not overdose the CO_2, and this was accomplished by sparging the CO_2 in portions with careful observation of the temperature. As soon as no exotherm was observed, the addition of CO_2 was stopped. A sample was then titrated with *n*-BuLi/fluorene in order to determine the excess CO_2, which was in our case 0.6 equiv. Using this information, the required amount LDA was determined. On our largest scale, 389 g of *rac-trans*-**30** was prepared, showing a 51% yield and containing less than 2% of the *cis* acid after 2-fold crystallization. Finally, *rac-trans*-**30** was resolved in EtOAc with (*R*)- and (*S*)-phenylglycinol in 29% and 15% yield, respectively. The solvent choice was crucial; EtOAc with 0.5% water was required to give good crystallization.[29]

Approach 2: Resolution by Chromatography. From previous experiments we learned that it is possible to resolve benzyl ester *rac-cis*-**25** into its enantiomers (*S*)- and (*R*)-*cis*-**25** by chromatography on a chiral stationary phase. In our second approach we planned to convert the enantiomerically pure *cis* compounds (*S*)- and (*R*)-*cis*-**25** to the (*R*)- and (*S*)-*trans*-**25** by epimerization followed by hydrogenation in order to obtain (*S*)- and (*R*)-*trans*-**30** (Scheme 6). We chose the benzyl ester because it made UV detection during chromatography easy, and we expected that the mild deprotection conditions would not affect the stereochemical integrity. We initially planned to synthesize the benzyl ester *rac-cis*-**25** directly by reacting the lithiated intermediate from step 1 with benzylchloroformate instead of CO_2. In contrast to the excellent *cis* selectivity for the reaction with CO_2, the use of benzylchloroformate led to significant formation of *trans* product *rac-trans*-**25**. The longer the reaction time and the higher the temperature after the electrophile addition, the lower the *cis*/*trans* ratio and the smaller the sum of *cis* and *trans* product compared to an internal standard. Due to this observed epimerization, we decided to follow a two-step protocol (Scheme 6, step 1). The benzylation was accomplished with the crude *rac-cis*-**30** using an excess of benzyl bromide/K_2CO_3 in acetone. After filtration and solvent exchange for ammonia in methanol, the benzyl bromide was converted to benzylamine to facilitate removal by acid extraction. Chromatography on silica gel provided 242 g of

Scheme 5. Approach 1: Resolution by Diastereomeric Salt Formation



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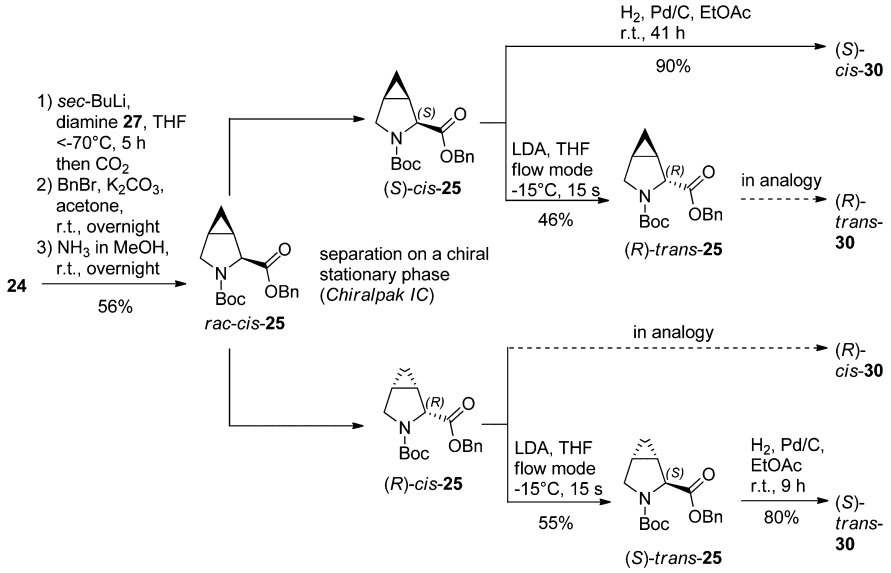
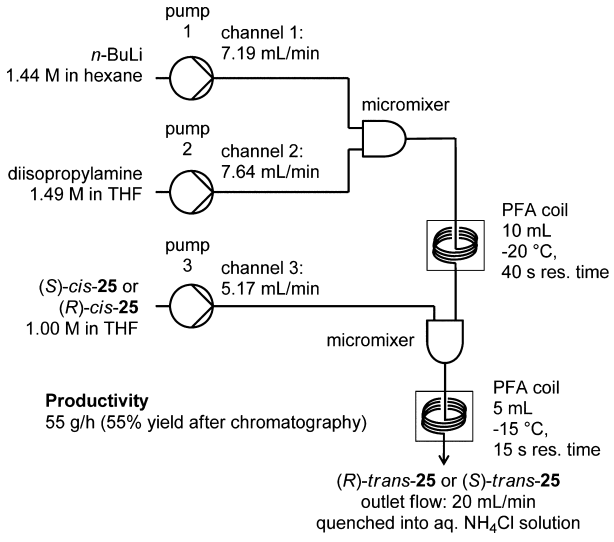
Scheme 6. Approach 2: Resolution by Chromatography



rac-cis-**25** in 58% yield. Next, we wanted to epimerize *rac-cis*-**25** to the *trans* ester *rac-trans*-**25**.

We identified LDA as the best base for the epimerization[30] and quickly learned that short reaction times were the key to success. The short reaction time of <60 s necessary for batch reactions[31] would have been challenging for scaling up, and we expected decreased yields for larger batches. With the aid of a commercially available flow machine (Scheme 7) we were able to achieve these very short reaction times and to produce 17 g of (*S*)-*trans*-**25** with a productivity of 55 g/h (55% yield).[32]

Scheme 7. Flow Setup for the Epimerization of (*S*)-*cis*-25 and 38 Using a Vapourtec Flow Machine



Other Approaches. As a mild alternative for the epimerization, we utilized aldehyde-promoted racemization via an iminium intermediate[33] on deprotected amines *rac-cis*-**31** and *rac-trans*-**31** (Scheme 8). Unfortunately, the thermodynamic equilibrium between *rac-cis*-**31** and *rac-trans*-**31** could not be pushed past 1:1.

The formation of esters or amides from Boc-protected anologue *rac-cis*-**30** using chiral alcohols or amines gave diastereoisomers that were potentially separable by crystallization or chromatography. However, the corresponding diastereomers obtained by coupling (−)-menthol, (−)-borneol, (+)-1-phenylethanol, and (−)-1-phenylethylamine with *rac-cis*-**30** showed poor separation by chromatography and were only obtained in yields between 27% and 49% after coupling with EDCI, DMAP, and NEt_3 in dichloromethane.

Stereochemical Assignment. We synthesized (*S*)-*trans*-**1** starting from L-pyroglutamic acid (**19**) following literature protocols (Scheme 2H)[14] and obtained (*S*)-*trans*-**25** after Boc protection. The sample of (*S*)-*trans*-**25** showed a negative optical rotation. A crystal structure of the (*R*)-phenylglycinol salt of (*R*)-*trans*-**30** confirmed the stereochemical assignments.

Origin of *cis* Selectivity. *Ab initio* calculations were carried out in order to explain the unexpected *cis* selectivity during the deprotonation and CO_2 addition sequence described (Scheme 5). The energy of the thermodynamic *trans* product *rac-trans*-**30** is 3.46 kcal/mol lower than the energy for the *cis* product *rac-cis*-**30**, which is in qualitative agreement with the observed 9:1 excess for *rac-trans*-**30** after complete epimerization. For the intermediate complex of **24** with lithium and diamine **27**, the *cis* conformation is 3.90 kcal/mol lower than the *trans* conformation. The lithium-coordinated complex without diamine **27** is 3.55 kcal/mol lower in energy than the *trans*, and this is in very good agreement with the sole formation of *cis* product *rac-cis*-**30**. The agreement between both basis set levels is very good, with relative energy differences between the lithium intermediate and the final structures of 0.12 and 0.16 kcal/mol and average root-mean-square deviation of 0.044 Å. The 3,7-dipropyl-3,7-diazabicyclo[3.3.1]nonane complex of the intermediate was calculated with the 6-311G** basis set only and with methyl carbamate instead of Boc, while the Li-only coordinated intermediate was calculated using the PVTZ basis set.

The structures of the energy-minimized *cis* and *trans* intermediate complexes are shown in Figure 1.

In the overlay, both complexes are very similar; that is, an almost perfectly planar Li−O═C−N−C−Li ring is the dominating structural motif. The energetic preference for *cis*-Li-**24** can be rationalized by comparing dihedral angles between substituents of the 5-rings: In the minimum energy *cis* structure,

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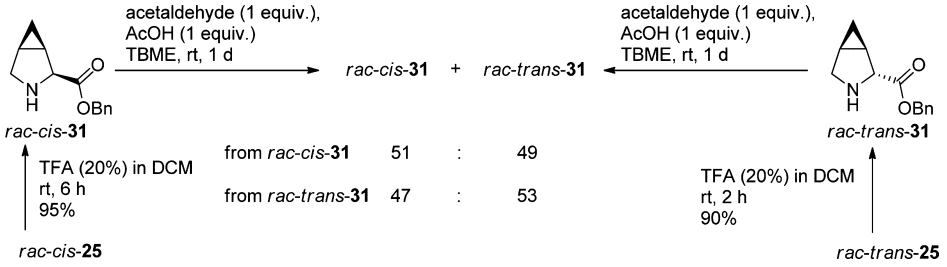
Scheme 8. Aldehyde-Promoted Epimerization via Iminium Intermediate



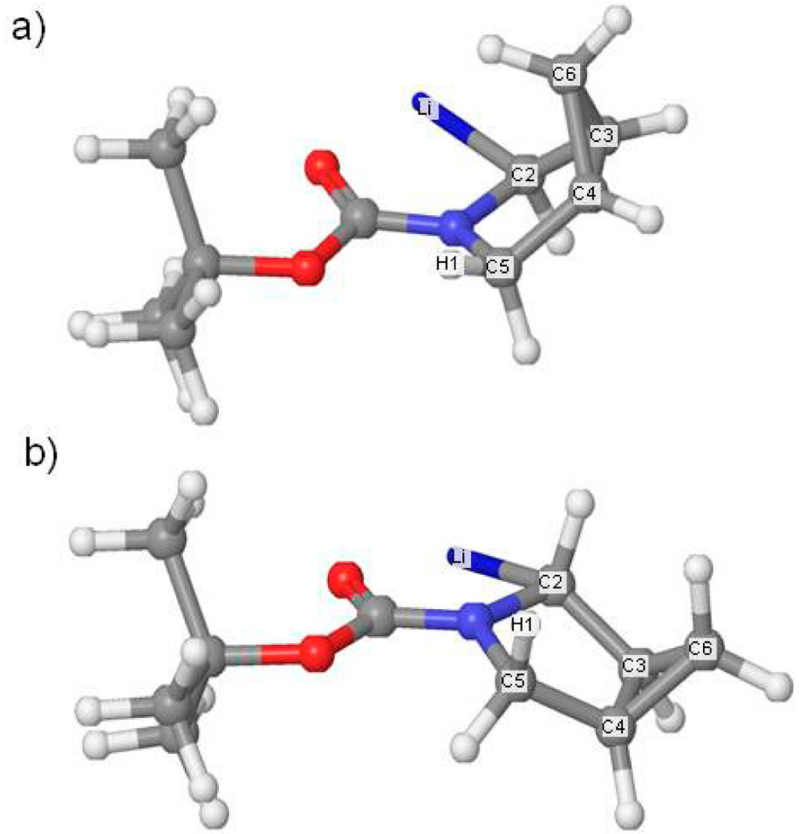


Figure 1. Energy-minimized (a) *cis* and (b) *trans* Li complex of **24** (diamine **27** not shown for clarity) with atom naming convention used for describing dihedrals.

the dihedral Li−C2−C3−C6 is 56.7°, the dihedral H−C2−C3−H is 48.9°, the dihedral H−C4−C5−H is 40.9°, and the dihedral C6−C5−C4−H1 is 70.2°. For the minimum energy *trans* structure, the dihedral Li−C2−C3−H is 16.9°, the dihedral H−C2−C3−C6 is 30.7°, the dihedral H−C4−C5−H is 8.4°, and the dihedral C6−C5−C4−H1 is 40.4°. Thus, the *trans* intermediate contains more eclipsed-like features, which are energetically less favorable than the more staggered conformations of the *cis* intermediate.

Our calculations indicated that the *cis* selectivity is introduced at the stage of the Li-**24**-diamine-**27** complex and then maintained through a CO_2-insertion mechanism with retention.

CONCLUSION

In conclusion we have developed a one-pot protocol for the synthesis of the *cis* and *trans* acids *rac-cis*-**30** and *rac-trans*-**30**, in 74% and 51% yield, respectively. They can be resolved via diastereomeric salt formation into all four isomers. Alternatively, one can form the benzyl ester from *rac-cis*-**30** followed by resolution on a chiral stationary phase. Hydrogenation of these benzyl esters delivered the enantiomerically pure acids (*R*)- and (*S*)-*cis*-**30** or, after epimerization, the enantiomerically pure acids (*R*)- and (*S*)-*trans*-**30**.

EXPERIMENTAL SECTION

General Procedures. All reagents were purchased and used as received unless otherwise noted. *tert*-Butyl 3-azabicyclo[3.1.0]hexane-3-carboxylate (**24**) and 3,7-dipropyl-3,7-diazabicyclo[3.3.1]nonane (**27**) were commercially available. The latter was distilled at 0.04 mbar and 80−115 °C prior to use. *cis*-3-(*tert*-Butoxycarbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (*rac-cis*-**30**) was commercially available and used (*N*-Boc protected)[21] for the resolution via diastereomeric salt formation. HPLC method 1: XDB-C18 column, 4.6 mm × 50 mm, 1.8 μm, using acetonitrile and water as eluent (both containing 0.05% TFA), column temperature of 35 °C, flow rate of 1.0 mL/min, detection at 216 nm. The standard gradient used was 5% to 100% acetonitrile over 6 min, 100% acetonitrile for 1.5 min, followed by 100% to 5% acetonitrile over 0.5 min. HPLC method 2 (for ee

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determination): IC (IC00CE-LB014, 250 × 4.6 mm, 5 um) column, 100% dichloromethane, column temperature 25 °C, flow rate of 1.0 mL/min, detection at 250 nm, run time 10 min. HPLC method 3 (for ee determination): AD-H (250 × 4.6 mm, 5 um) column, hexane/2-PrOH 93:7 + 0.1% TFA, column temperature rt, flow rate of 0.5 mL/min, detection at 210 nm, run time 40 min. HPLC method 4 (for ee determination): IC (250 × 4.6 mm, 5 um) column, heptanes/EtOH/MeOH 90:5:5 + 0.1% TFA, column temperature rt, flow rate 1 mL/min, detection at 210 nm, run time 20 min. Purities were characterized with area % at the wavelength declared for the method used. GC: Silaren column (30 m × 0.32 mm i.d., 0.12 μm film). The standard 12 min run started at 40 °C, which was held for 0.3 min, followed by a temperature ramp at 25 °C/min up to 220 °C and a second ramp of 40 °C/min up to 280 °C, at which the temperature was held for 3 min. The hydrogen flow was 2 mL/min, the front inlet temperature was 220 °C, and the front detection temperature was 300 °C. LC-MS method 1: Acquity HSS T3 1.8 μm 2.1 × 50 mm column at 50 °C. Eluent A: water + 0.05% formic acid + 3.75 mM ammonium acetate; eluent B: acetonitrile + 0.04% formic acid. Gradient: from 2% to 98% B in 1.4 min with a flow rate of 1.2 mL/min, detection at 215 nm. NMR was performed using a 400 MHz machine. ^{1}H shifts were referenced to DMSO-d_6 at 2.49 ppm and $CDCl_3$ at 7.26 ppm. ^{13}C shifts were referenced to DMSO-d_6 at 39.52 ppm and $CDCl_3$ at 77.16 ppm. High-resolution mass spectrometry (HRMS) was performed using QTOF with Classic Acquity UPLC with PDA. Elemental analyses were performed externally, complying with the ISO 9001 standard. Glass vessels for small-scale lithiation reactions were heated to >150 °C and cooled *in vacuo* or in a stream of argon. Specifications of the Vaportec flow equipment were described earlier by our group;[34] we used the following micromixer: "Comet X-01" from Techno Applications Co., Ltd.,Tokyo, Japan).

***Ab Initio* Calculations.** All calculations were done using Jaguar version 7.9 (Suite 2012, Schrödinger, LLC, New York, NY, 2012). Geometries were initially optimized using the M06-2X DFT method at the 6-311G** basis set.[35] Where possible, the key structures were fully reoptimized using the M06-2X functional at the PVTZ basis set level, as recommended by Schenker et al.[36]

***cis*-2-Benzyl 3-*tert*-Butyl-3-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (*rac-cis*-25).** Equipment: Büchi 30 L hastelloy reactor (CR30) with FlexyALR Systag control. To a solution of 250 g (1.36 mol) of *tert*-butyl 3-azabicyclo[3.1.0]hexane-3-carboxylate (**24**) and 360 g (1.71 mol, 1.25 equiv) of 3,7-dipropyl-3,7-diazabicyclo[3.3.1]-nonane (**27**) in 5 L of dry THF at −84 °C was added within 15 min 1.46 L (2.05 mol, 1.5 equiv) of *sec*-BuLi solution (1.4 M in cyclohexane). The progress of deprotonation was monitored with GC (quenching of a sample with excess benzaldehyde). After 3 h at −85 °C a mixture of dry CO_2 gas was sparged through the reaction mixture in such a manner that the internal temperature did not exceed −76 °C. To the reaction mixture were added 2 L of 20% $KHSO_4$ solution (until pH = 7) and 5 L of water, and the reaction solution was warmed to ambient temperature. After 4 L of THF was distilled off, the pH was lowered to 4 and the residue was extracted three times with a total of 7 L of MTBE. The combined organic phases were dried over sodium sulfate, filtered, and concentrated to yield 259.8 g of a dark brown oil. This was dissolved in 5 L of acetone at rt, to which were added 173 g (1.25 mol) of potassium carbonate and 135 mL (1.14 mol) of benzyl bromide. The reaction mixture was stirred at rt overnight. The white suspension was filtered over Celite and concentrated to give 357 g of a dark, brown oil, which was stirred with 1 L of heptanes for 1 h at rt, filtered, and concentrated to give 330 g of oil (with this step the most polar impurities were removed). In order to remove excess benzyl bromide, the crude product was dissolved in 1.6 L of THF; then 320 mL of a 7 N ammonia solution in MeOH was added and the reaction mixture stirred at 40 °C for 6 h. The reaction mixture was concentrated and treated with 2 L of 10% $KHSO_4$ solution, 1 L of crushed ice, and 2 L of MTBE. The aqueous phase was extracted twice with each 0.8 L of MTBE. The combined organic phases were dried over sodium sulfate, filtered, and concentrated to yield 286 g of an orange-brown oil. The crude product was purified on a 2 kg silica gel column (5 injections) with an EtOAc/heptanes gradient to yield 242 g (56% yield over two steps) of *cis*-acid benzyl ester. Purity: >97% (HPLC method 1). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.38−7.32 (m, 5H), 5.19−5.07 (m, 2H), 4.35−4.34 (m, 1H), 3.49−3.44 (m, 1H), 3.37 (d, J = 10.4, 1H), 1.93−1.87 (m, 1H), 1.68−1.62 (m, 1H), 1.33 and 1.23 (2s, 2 rotamers 4:6, 9H), 0.66−0.61 (m, 1H), 0.52−0.47 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.7, 170.2, 154.1, 153.3, 136.1, 135.8, 128.5, 128.4, 128.2, 127.9, 127.7, 79.2, 66.0, 65.6, 60.2, 60.0, 49.6, 49.5, 28.0, 27.7, 20.5, 19.4, 16.3, 15.6, 8.3, 8.1 (rotamers). ^{1}H NMR (600 MHz, DMSO-d_6, 100 °C): δ 7.41−7.31 (m, 5H), 5.20−5.13 (m, 2H), 4.38 (d, J = 5.3 Hz, 1H), 3.52 (dd, J = 10.4, 5.0 Hz, 1H), 3.40 (d, J = 10.5 Hz, 1H), 1.96−1.90 (m, 1H), 1.71−1.64 (m, 1H), 1.34 (s, 9H), 0.68−0.63 (m, 1H), 0.58−0.54 (m, 1H). LC-MS method 1: t_R =1.19 min, m/z 262 $[M - \text{butene} + H]^+$, 318 $[M + H]^+$, 335 $[M + NH_4]^+$, 652 $[2M + NH_4]^+$. HRMS (ESI): calcd for $C_{18}H_{23}NO_4Na$ $[M + Na]^+$ 340.1525, found 340.1534.

Chromatographic Resolution of *cis*-2-Benzyl 3-*tert*-Butyl-3-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (*rac-cis*-25). A 203.3 g batch of the racemic *cis*-benzyl ester *rac-cis*-**25** was resolved. Preparative method: IC 250 × 76 mm, 20 um; 100% dichloromethane; 270 mL/min at 25 °C; detection at 250 nm. Analytical method: IC (IC00CE-LB014, 250 × 4.6 mm, 5 um); 100% dichloromethane; 1 mL/min at 25 °C, detection at 250 nm. First eluting compound was the (−)-enantiomer; the second eluting compound, the (+)-enantiomer.

(−)-*cis*-(1*R*,2*S*,5*S*)-2-Benzyl 3-*tert*-Butyl-3-azabicyclo[3.1.0]-hexane-2,3-dicarboxylate ((*S*)-*cis*-25). A 104.0 g (51% recovery) amount of a colorless, viscous oil was obtained. The compound partially crystallized after several months. Mp: 42−45 °C. Purity (HPLC method 1, t_R = 5.53 min): 90.0%. Enantiopurity (HPLC method 2, t_R = 4.26 min) > 99.9% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38−7.31 (m, 5H), 5.19−5.06 (m, 2H), 4.35−4.34 (m, 1H), 3.49−3.43 (m, 1H), 3.39−3.36 (m, 2H, partially overlaid by H_2O signal), 1.93−1.85 (m, 1H), 1.67−1.61 (m, 1H), 1.35 and 1.23 (2s, 2 rotamers 3:5, 9H), 0.66−0.59 (m, 1H), 0.51−0.46 (m, 1H). $[\alpha]^{24}_D$ = −106 (c 0.5, $CHCl_3$).

(+)-*cis*-(1*S*,2*R*,5*R*)-2-Benzyl 3-*tert*-Butyl-3-azabicyclo[3.1.0]-hexane-2,3-dicarboxylate ((*R*)-*cis*-25). A 99.3 g (49% recovery) amount of a colorless, viscous oil was obtained. Purity (HPLC method 1, t_R = 5.53 min): 98.5%. Enantiopurity (HPLC method 2, t_R = 5.77 min): >99.9% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38−7.31 (m, 5H), 5.19−5.06 (m, 2H), 4.35−4.34 (m, 1H), 3.49−3.40 (m, 1H), 3.37−3.36 (m, 2H, partially overlaid by H_2O signal), 1.93−1.85 (m, 1H), 1.67−1.61 (m, 1H), 1.35 and 1.23 (2s, 2 rotamers 3:5, 9H), 0.66−0.60 (m, 1H), 0.51−0.46 (m, 1H). HRMS (ESI): calcd for $C_{18}H_{23}NO_4Na$ $[M + Na]^+$ 340.1525, found 340.1534. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 67.27; H, 7.08; N, 4.26. $[\alpha]^{24}_D$ = +108 (c 0.6, $CHCl_3$).

***trans*-2-Benzyl 3-*tert*-Butyl-3-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (*rac-trans*-25) in Batch Mode.** Preparation of the LDA solution: In a 10 mL round-bottom flask under argon containing 4.55 mL (6.78 mmol, 2.2 equiv) of a 1.49 M diisopropylamine solution in THF was added at 0 °C 4.14 mL (6.16 mmol, 2.0 equiv) of a 1.49 M BuLi solution in hexane (freshly titrated). After 5 min this solution was cooled in a dry ice/acetone bath to −36 °C. The LDA solution was then quickly transferred via cannula to a solution of 0.98 g (3.08 mmol) of racemic *cis*-benzyl ester *rac-cis*-**25** in 15.4 mL of THF, which was cooled to −32 °C. The internal temperature of the reaction mixture immediately increased from −32 to −21 °C and then decreased again. After 60 s of intense stirring the reaction mixture (−23 °C) was quenched with 25 mL of saturated aqueous $NaHCO_3$ solution and warmed to rt. After addition of 30 mL of water the mixture was extracted three times with EtOAc. The combined organic phases were washed with brine, dried over sodium sulfate, and concentrated to yield 0.97 g of an oil. This was purified on 100 g of silica gel with EtOAc/heptanes to yield 36 mg (3.7% yield) of the starting material and 0.69 g (71% yield) of product *rac-trans*-**25** as a colorless, viscous oil, which crystallized after a few days upon standing. Mp: 49−53 °C. Purity (HPLC method 1, t_R = 5.67 min): 89.5% (looked pure in ^{1}H NMR). ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.38−7.32 (m, 5H), 5.22−5.10 (m, 2H), 4.25 and 4.19 (2s, 1H, 2 rotamers),

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3.43−3.39 (m, 2H), 1.64−1.58 (m, 2H), 1.35 and 1.22 (2s, 2 rotamers, 9H), 0.76−0.73 (m, 1H), 0.26−0.26 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 171.6, 171.4, 154.1, 153.7, 135.8, 128.5, 128.4, 128.2, 128.1, 127.7, 79.3, 79.1, 66.1, 66.0, 61.2, 60.9, 48.3, 48.3, 28.0, 27.8, 19.6, 18.7, 15.3, 14.5, 9.0, 8.8 (rotamers). LC-MS method 1: t_R =1.24 min; m/z 262 $[M - \text{butene} + H]^+$, 318 $[M + H]^+$, 335 $[M + NH_4]^+$, 652 $[2M + NH_4]^+$. HRMS (ESI): calcd for $C_{18}H_{23}NO_4Na$ $[M + Na]^+$ 340.1525, found 340.1536.

(−)-*trans*-(1*S*,2*S*,5*R*)-2-Benzyl 3-*tert*-Butyl-3-azabicyclo-[3.1.0]hexane-2,3-dicarboxylate ((*S*)-*trans*-25) in Flow Mode. The flow reactor was configured using a combination of the R2C pump module and R4 chiller module. A 10 mL and a 5 mL PFA tubing (internal diameter 1 mm) reactor were installed in the R4 module, along with an 8 bar ceramic back-pressure regulator fitted in-line between the reactor outflow and the collection valve. The solvent bottle was filled with anhydrous THF, and the reagent stock bottles were filled with *n*-BuLi in hexane (1.44 M), diisopropylamine in THF (1.49 M), and substrate (*R*)-*cis*-**25** in THF (1.00 M), respectively (Scheme 7). Pump 1 delivered 7.19 mL/min *n*-BuLi solution (2.0 equiv) and pump 2 delivered 7.64 mL/min diisopropylamine solution (2.2 equiv) through the 10 mL reactor with a residency time of 40 s at −20 °C. The outlet flow of this LDA solution (14.83 mL/min) was combined with the substrate flow (1.0 equiv) delivered from pump 3 at 5.17 mL/min through the 5 mL reactor to give a residency time of 15 s at −15 °C. The second Y-piece (between the two reactors) was immersed into an external cooling bath and kept at −20 °C. The outlet stream was collected for 18 min (365 mL) and poured into 400 mL of a well-stirred aqueous 10% ice cold NH_4Cl solution. This was then extracted three times with 150 mL of MTBE. The combined organic phases were washed with brine, dried over sodium sulfate, and concentrated to give 27.1 g of an orange oil. The *cis*/*trans* ratio of the two benzyl esters was 3:97. The crude product was purified on 2 kg of silica gel (heptanes/EtOAc) to yield 16.83 g (56% yield) of the (−)-*trans* benzyl ester (*S*)-*trans*-**25** as a pale yellow, viscous oil. Purity (HPLC method 1, t_R = 5.68 min): 98.7%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38−7.30 (m, 5H), 5.23−5.09 (m, 2H), 4.25 and 4.19 (2s, 2 rotamers, ratio 2:3, 1H), 3.44−3.39 (m, 2H), 1.65−1.54 (m, 2H), 1.35 and 1.22 (2s, 2 rotamers, ratio 2:3, 9H), 0.77−0.71 (m, 1H), 0.25−0.20 (m, 1H). $[\alpha]^{24}_D$ = −83.4 (c 0.5, $CHCl_3$).

(+)-*trans*-(1*R*,2*R*,5*S*)-2-Benzyl 3-*tert*-Butyl-3-azabicyclo-[3.1.0]hexane-2,3-dicarboxylate ((*R*)-*trans*-25) in Flow Mode. The same procedure was applied as for (*S*)-*trans*-**25** but with (*S*)-*cis*-**25** as the starting material. However, the first reactor clogged and had to be cleaned. As a consequence, the yield was lower at 46%. (*R*)-*trans*-**25** (12.0 g) was obtained as a pale yellow, viscous oil. Purity (HPLC method 1, t_R = 5.68 min): 95.5%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38−7.30 (m, 5H), 5.23−5.09 (m, 2H), 4.25 and 4.19 (2s, 2 rotamers, ratio 2:3, 1H), 3.44−3.36 (m, 2H), 1.65−1.54 (m, 2H), 1.35 and 1.22 (2s, 2 rotamers, ratio 2:3, 9H), 0.77−0.71 (m, 1H), 0.26−0.26 (m, 1H). $[\alpha]^{24}_D$ = +75.5 (c 0.6, $CHCl_3$).

Determination of the *cis*/*trans* Ratio of *cis*/*trans*-30 via Benzyl Ester Formation. *General Procedure.* To 50 mg (ca. 0.2 mmol) of acid **30** or 0.5 mL of the reaction mixture (concentrated) were added 0.2 mL of BnBr, 0.25 g of potassium carbonate, and 3 mL of acetone. After stirring for at least 2 h at rt the *cis*/*trans* ratio of the benzyl ester **25** was determined with HPLC method 1.

***cis*-3-(*tert*-Butoxycarbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic Acid (*rac*-*cis*-30): Method A.** Equipment: 400 mL reaction flask with four necks and mechanical stirrer, internal thermometer, and argon inlet. To a solution of 12 g (65.5 mmol) of *tert*-butyl 3-azabicyclo[3.1.0]hexane-3-carboxylate (**24**) and 17.2 g (82 mmol, 1.25 equiv) of **27** in 262 mL of dry THF, with the temperature kept below −60 °C, was added 56.1 mL (79 mmol, 1.2 equiv) of *sec*-BuLi solution (1.4 M in cyclohexane) over 12 min. The progress of deprotonation was checked with GC (quenching of a sample with excess benzaldehyde). After 5 h at −60 °C the reaction mixture was cooled to −68 °C and dry CO_2 gas was sparged through the reaction mixture. The internal temperature went up to −45 °C within 1−2 min. To the reaction mixture was added ca. 150 mL of water (pH > 10). Most of the THF was distilled off, and the aqueous phase extracted twice with 150 mL of MTBE. To the aqueous phase were added ca. 300 mL of 25% aqueous $KHSO_4$ solution and ice until the pH was <3; then it was extracted three times with 200 mL of MTBE. The combined organic phases were washed with 200 mL of brine, dried over sodium sulfate, filtered, and concentrated. Some dichloromethane was added, and the product completely dried on vacuum overnight to yield 11.6 g of *rac*-*cis*-**30** (78%) as an almost colorless resin that solidified during 1 week (a 3 L round-bottom flask was used due to strong foaming on drying). The purity according to the ^{1}H NMR ($CDCl_3$) was estimated as >95%. No *trans* acid could be detected (as its benzyl esters). Mp: 119−124 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.4 (br, 1H), 4.18−4.14 (m, 1H), 3.47−3.31 (m, ?H, together with H_2O signal), 1.88−1.81 (m, 1H), 1.65−1.58 (m, 1H), 1.35 and 1.30 (2s, 2 rotamers ca. 2:3, 9H), 0.64−0.58 (m, 1H), 0.52−0.49 (m, 1H). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (br, 1H), 4.43−4.35 (m, 1H), 3.63−3.55 (m, 2H), 1.93−1.87 (m, 1H), 1.68−1.62 (m, 1H), 1.44 and 1.40 (2s, 2 rotamers ca. 1:2, 9H), 0.79−0.68 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.5, 80.7, 80.6, 60.5, 60.4, 50.0, 49.7, 28.3, 28.2, 20.6, 19.7, 16.7, 16.1, 8.64, 8.56 (rotamers). HRMS (ESI): calcd for $C_{11}H_{16}NO_4$ $[M - H]^-$ 226.1079, found 226.1087. Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.24; H, 7.38; N, 6.15.

***cis*-3-(*tert*-Butoxycarbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic Acid (*rac*-*cis*-30): Method B.** Equal to method A but instead of **27** 12.18 g (105 mmol, 1.6 equiv) of TMEDA was used. *rac*-*cis*-**30** (12.1 g, 81% yield) as an almost colorless resin was obtained. According to ^{1}H NMR the compound contained 15% MTBE. Benzylation of a small sample revealed the existence of 2% of the *trans* acid and 22% of a diacid. On the basis of these data the purity was estimated to be 60%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.18−4.14 (m, 1H), 3.48−3.27 (m, ?H, overlaid by a broad signal from 4.0 to 3.2 ppm), 1.88−1.82 (m, 1H), 1.65−1.53 (m, 1H), 1.35 and 1.30 (2s, 2 rotamers ca. 2:3, 9H), 0.65−0.58 (m, 1H), 0.52−0.49 (m, 1H).

***cis*-3-(*tert*-Butoxycarbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic Acid (*rac*-*cis*-30): Diamine-Free Deprotonation.** Equipment: 50 mL three-neck flask with magnetic stirrer, internal thermometer, and argon inlet. To a solution of 0.5 g (2.73 mmol) of *tert*-butyl 3-azabicyclo[3.1.0]hexane-3-carboxylate (**24**) in 19 mL of dry THF at −40 °C was added dropwise 2.53 mL (3.55 mmol, 1.3 equiv) of *sec*-BuLi solution (1.4 M in cyclohexane). The bright yellow reaction mixture was stirred between −45 and −38 °C. The progress of deprotonation was monitored with GC (quenching of a sample with excess benzaldehyde) after 2 and 5 h (in both cases mostly starting material was detected). Dry CO_2 gas was then sparged through the reaction mixture. The internal temperature went up to −36 °C; then the reaction mixture was allowed to warm to rt, when its consistency became jelly-like. The workup was identical to that described for method A. A 486 mg amount of starting material was recovered from the basic extraction, and 23 mg of a colorless resin was obtained after extraction at pH < 3 and benzylated for HPLC analysis. Neither *cis* nor *trans* benzyl ester was detectable; the major signal corresponded to the bis-benzylated diester (**26**).

Salt Screen. Resolution of Racemic Acids via Formation of Diastereomeric Salts. *General Procedure.* A total of 192 combinations consisting of 16 chiral bases and 12 solvents were applied. For each combination 0.05 mmol of racemic acid and a stoichiometric amount of a chiral base were used in a concentration range starting from maximum 250 down to 25 mM. The following bases were used: (*S*)-(−)-1-phenylethylamine, (−)-ephedrine, (+)-pseudoephedrine, (−)-norephedrine, (*R*)-(−)-2-amino-1-butanol, (*R*)-(−)-phenylglycinol, (*S*)-(+)-1,2,3,4-tetrahydro-1-naphthylamine, brucine, strychnine, (+)-cinchonin, (−)-cinchonidine, (+)-quinidine, quinine, L-lysine, (+)-dehydroabietylamine 60%, (1*R*,2*R*)-(−)-1,2-diaminocyclohexane. The following solvents were used: water, EtOH/water 50:50, EtOH/water 96:4, EtOH absolute, MeOH, 2-PrOH, acetone, 2-butanone, EtOAc, EtOAc saturated with water, acetone/$CHCl_3$ (1:1), acetonitrile. The chiral bases as well as the racemic acid were distributed as freshly prepared solutions in MeOH or dichloromethane into 192 × 2 mL HPLC vials. After removal of the solvent the 12 different solvents were added and the vials closed with a

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lid. After heating at 80 °C for 1−2 h (manual shaking from time to time) the vials containing clear solutions were placed on a second plate and allowed to cool to rt. To the remaining vials were added solvents in 0.2 to 0.5 mL portions, and the heating and picking steps repeated until the vials were full. After a day, sometimes longer, crystals were separated from the mother liquor (filtered or decanted, no washing) and dried *in vacuo*. In a second round the vials were stored at 6 °C for a few days and new crystals collected. The yields were calculated based on the weight assuming a 1:1 salt was formed, and the ee's determined via HPLC (the acid was liberated before).

Salt Screen of *rac-cis*-30. The best results were obtained with (a) (*R*)-(−)-phenylglycinol in EtOAc (c = 250 mM), crystals collected at 6 °C, yield 33%, enantiopurity (HPLC method 3, t_R = 16.65 min) 71% ee; (b) brucine in water (c = 14 mM), crystals collected at 24 °C, yield 32%, enantiopurity (HPLC method 3, t_R = 17.56 min) 71% ee; (c) (−)-cinchonidine in acetonitrile (c = 250 mM), crystals collected at 6 °C, yield 46%, enantiopurity (HPLC method 3, t_R = 16.65 min) 78% ee; (d) (+)-dehydroabietylamine in 2-butanone (c = 63 mM), crystals collected at 24 °C, yield 53%, enantiopurity (HPLC method 3, t_R = 17.56 min) 60% ee; (e) (+)-dehydroabietylamine in EtOAc saturated with water (c = 31 mM), crystals collected at 24 °C, yield 32%, enantiopurity (HPLC method 3, t_R = 17.56 min) 99% ee. Condition (e) was used to obtain the (−)-enantiomer followed by condition (c) for the (+)-enantiomer.

Salt Screen of *rac-trans*-30. The best results were obtained with (a) (*R*)-(−)-phenylglycinol in EtOAc (c = 55 mM), crystals collected at 6 °C, yield 56%, enantiopurity (HPLC method 4, t_R = 7.06 min) 74% ee; (b) (*R*)-(−)-phenylglycinol in acetone/$CHCl_3$ (1:1) (c = 250 mM), crystals collected at 6 °C, yield 32%, enantiopurity (HPLC method 4, t_R = 7.06 min) 93% ee; (c) (1*R*,2*R*)-(−)-1,2-diaminocyclohexane in 2-butanone (c = 250 mM), crystals collected at 24 °C, yield 29%, enantiopurity (HPLC method 4, t_R = 7.06 min) 89% ee. Condition (a) was used to obtain the (+)-enantiomer followed by condition (a) using (*S*)-(+)-phenylglycinol for the (−)-enantiomer.

(−)-*cis*-(1*R*,2*S*,5*S*)-3-(*tert*-Butoxycarbonyl)-3-azabicyclo-[3.1.0]hexane-2-carboxylic Acid ((*S*)-*cis*-30) via Diastereomeric Salt Formation. To a well-stirred solution of 121.5 g (0.54 mol) of *rac-cis*-**30** in 20 L of EtOAc (saturated with water) was added a solution of 164 g (0.52 mol) of 90% pure (+)-dehydroabietylamine in 4 L of EtOAc (saturated with water) at rt. After the addition a precipite formed. The suspension was heated to reflux for 1 h. The clear solution was cooled to 20 °C over 3 h. A pale brown suspension was obtained, which was stirred for another 3 h. After filtration the filter cake was washed twice with 2 L of cold EtOAc and dried 18 h at 10 mbar and 30 °C. An 86 g amount of the dehydroabietylamine salt was obtained. Mp: 213−219 °C. Anal. Calcd for $C_{31}H_{48}N_2O_4$: C, 72.62; H, 9.44; N, 5.46. Found: C, 72.29; H, 9.06; N, 5.37. $[\alpha]^{23}_D$ = −33.3 (c 0.50, MeOH). To a well-stirred suspension of 95 g of dehydroabietylamine salt (combined with a trial batch) in 3 L of deionized water were added 60 g of potassium carbonate and 3 L of MTBE. After 5 min the two clear phases were separated. The aqueous phase was extracted twice with 1 L of MTBE. The combined organic phases were extracted twice with 0.5 L of water, dried over magnesium sulfate, filtered, and concentrated to yield 70 g of a brown oil of recovered dehydroabietylamine. To the combined aqueous phases, while vigorously stirred, were added 3 L of EtOAc and 150 g of citric acid. After 10 min the aqueous phase was separated and extracted two more times with 1 L of EtOAc. The combined organic phases were washed twice with 1 L of water, dried over magnesium sulfate, filtered, and concentrated at 45 °C *in vacuo*. The resulting resin was triturated with low-boiling petroleum ether for 1 h in order to crystallize. The solid was filtered off and dried at 50 °C for 5 h at 1 mbar to yield 38.6 g (32% yield, based on 100 g of *rac-cis*-**30**) of colorless, crystalline (*S*)-*cis*-**30**. Mp: 89−91 °C. Enantiopurity (HPLC method 3, t_R = 17.56 min): >99% ee. ^{1}H NMR (600 MHz, DMSO-d_6): δ 12.41 (s, 1H), 4.19−4.16 (m, 1H), 3.47−3.42 (m, 1H), 3.35 (d, J = 10.1 Hz, 1H), 1.88−1.83 (m, 1H), 1.65−1.60 (m, 1H), 1.36 and 1.31 (2s, 2 rotamers ca. 1:2, 9H), 0.64−0.60 (m, 1H), 0.53−0.50 (m, 1H). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.85; H, 7.09; N, 6.16. $[\alpha]^{20}_D$ = −121.7 (c 1.0, $CHCl_3$). The mother liquor of the first crystallization was concentrated to give 207 g of a pale brown resin, which was suspended in 3 L of water. After the addition of 130 g of potassium carbonate and 3 L of MTBE, 75 g (+)-enantio-enriched (*R*)-*cis*-**30** was isolated in analogy to the above procedure. **Via Hydrogenation of Benzyl Ester (*S*)-*cis*-25.** (*S*)-*cis*-**25** (6.37 g, 17.7 mmol) was dissolved in 90 mL of EtOAc, and 0.94 g of Pd/C 10% was added. The reaction mixture was hydrogenated for 41 h at rt and atmospheric pressure. The catalyst was filtered off, and the product solution extracted with 150 mL of saturated aqueous $NaHCO_3$ solution. The aqueous phase was extracted with another 100 mL of EtOAc; then the pH was lowered by addition of citric acid and again extracted with 3 × 100 mL of EtOAc. These three EtOAc portions were combined, washed with brine, dried over sodium sulfate, and concentrated to yield 3.61 g (90% yield) of (*S*)-*cis*-**30** as a colorless resin, which started to crystallized after one week. Mp: 85−88 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.39 (s, 1H), 4.18−4.14 (m, 1H), 3.47−3.41 (m, 1H), 3.35−3.33 (m, overlaid by H_2O signal, ca. 2H), 1.89−1.81 (m, 1H), 1.65−1.58 (m, 1H), 1.35 and 1.30 (2s, 2 rotamers, ratio 3:5, 9H), 0.64−0.58 (m, 1H), 0.52−0.49 (m, 1H). $[\alpha]^{24}_D$ = −128.7 (c 0.53, $CHCl_3$).

(+)-*cis*-(1*S*,2*R*,5*R*)-3-(*tert*-Butoxycarbonyl)-3-azabicyclo-[3.1.0]hexane-2-carboxylic Acid ((*R*)-*cis*-30) via Diastereomeric Salt Formation. To 73.0 g of the enantio-enriched (*R*)-*cis*-**30** in 2 L of acetonitrile was added 95 g of (−)-cinchonidine. While heating to reflux, the suspension turned into a yellow solution. The oil bath was removed and the solution allowed to cool to rt. After a few hours the crystals were filtered and washed with 0.5 L of cold acetonitrile. The wet crystals were recrystallized in 1.3 L of acetonitrile to yield 103.7 g of the cinchonidine salt after drying at 45 °C *in vacuo*. Mp: 154.1−155.8 °C. Anal. Calcd for $C_{30}H_{39}N_3O_5$: C, 69.07; H, 7.54; N, 8.06. Found: C, 68.86; H, 7.35; N, 7.95. $[\alpha]^{23}_D$ = −16.3 (c 0.52, MeOH). The salt was suspended in a solution of 4 L of deionized water and 63 g of citric acid and then extracted with 6 L of MTBE. The MTBE phase was washed twice with 2 L of water. The combined aqueous phases were extracted twice with 2 L of MTBE. The combined organic phases were dried over magnesium sulfate, filtered, and concentrated to yield 44.3 g of a greenish resin, which crystallized after trituration in 500 mL of warm heptanes. After standing overnight at rt, the crystals were filtered, washed twice with 100 mL of cold heptanes, and dried to yield 34.0 g of crystalline (*R*)-*cis*-**30** (35% yield, based on 100 g *rac-cis*-**30**). Mp: 82−84 °C. Enantiopurity (HPLC method 3, t_R = 16.65 min): 97.4% ee. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.38 (s, 1H), 4.18−4.14 (m, 1H), 3.47−3.40 (m, 1H), 3.35−3.30 (m, 1H), 1.88−1.81 (m, 1H), 1.64−1.57 (m, 1H), 1.34 and 1.29 (2s, 2 rotamers ca. 1:2, 9H), 0.64−0.58 (m, 1H), 0.52−0.49 (m, 1H). Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 57.92; H, 7.06; N, 6.28. $[\alpha]^{24}_D$ = +121.4 (c 1.0, $CHCl_3$).

(+)-*cis*-(1*S*,2*R*,5*R*)-3-(*tert*-Butoxycarbonyl)-3-azabicyclo-[3.1.0]hexane-2-carboxylic Acid ((*R*)-*cis*-30) via Enantioselective Deprotonation. Equipment: 100 mL reaction flask with four necks and mechanical stirrer, internal thermometer, and argon inlet. A 5.4 g (23.1 mmol, 1.25 equiv) amount of (−)-sparteine (distilled prior to use) was placed into the reaction flask and diluted with 230 mL of dry diethyl ether. This 0.1 M solution was cooled below −70 °C; then 16.5 mL (23.06 mmol, 1.25 equiv) of a 1.4 M *sec*-BuLi solution in cyclohexane was added within 5 min. After being stirred for 15 min below −70 °C a solution of 3.38 g (18.45 mmol, 1 equiv) of 3-azabicyclo[3.1.0]hexane-3-carboxylic acid *tert*-butyl ester (**24**) in 15 mL of diethyl ether was added to the reaction mixture with a syringe. The pale yellow reaction mixture was stirred under argon overnight. After 38 h at −78 °C dry CO_2 gas was sparged through the reaction mixture for 3 min. The temperature immediately went up to −68 °C. The reaction mixture was allowed to warm to rt; then 25 mL of saturated aqueous Na_2CO_3 solution was added and the two phases were separated (another 70 mL of water had to be added in order to dissolve precipitated salts). The aqueous phase was extracted with 60 mL of MTBE, and the organic phase discarded. The pH of the aqueous phase was set at <3 with 25% aqueous $KHSO_4$ solution, and then the aqueous phase extracted three times with 60 mL of MTBE.

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The combined organic phases were washed with brine, dried over sodium sulfate, filtered, and concentrated to yield 1.53 g (37% yield) of product as a colorless resin, which contained 11% MTBE (according to ^{1}H NMR). Enantiopurity (HPLC method 3, t_R = 15.85 min): 73% ee. $[\alpha]^{24}_D$ = +68 (*c* 1.5, $CHCl_3$). 98% of the sparteine was recovered.

***trans*-3-(*tert*-Butoxycarbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic Acid (*rac-trans*-30).** Equipment: Büchi 30 L hastelloy reactor (CR30) with FlexyALR Systag control. Procedure: The reactor was inertized with argon. To a cooled solution of *tert*-butyl 3-azabicyclo[3.1.0]hexane-3-carboxylate (**24**) (600 g, 3.27 mol) and 3,7-dipropyl-3,7-diazabicyclo[3.3.1]nonane (**27**) (867 g, 4.12 mol) in 13 L of THF at −80 °C was pumped *sec*-BuLi (1.4 M in cyclohexane, 2.88 L, 4.03 mol) within 45 min, not allowing the internal temperature to exceed −75 °C. After the complete addition the pump was purged with 0.5 L of THF and the reaction mixture was warmed to −57 °C within 30 min and stirred at this temperature. The color turned from bright yellow to dark orange-brown during this time. IPC samples were taken as follows: With a pipet that was cooled in the reaction mixture a 1 mL aliquot was taken and poured into 1.5 mL of methyl iodide. After 2 min this mixture was extracted with 10 mL of MTBE and 2 mL of water, and the organic phase was filtered through a plug of sodium sulfate and analyzed by GC. After 5 h the ratio of starting material to methylated starting material was 3:7 (the same ratio was already observed after 4 h). Therefore, a second portion of *sec*-BuLi (0.320 L, 0.45 mol) was added. However, 1 h later the ratio did not change. A stream of dry CO_2 gas was sparged through the reaction mixture. After the internal temperature went up from −57 to −42 °C within a few minutes, the CO_2 stream was switched off (the jacket temperature was kept constant at −60 °C) and the internal temperature allowed to decrease to −47 °C. The CO_2 was switched on again followed by a second exotherm. At −40 °C the CO_2 was switched off and on again. No exotherm was observed anymore, and the reaction was assumed to be complete. The reaction mixture was purged with argon for 10 min and kept at −50 °C overnight (not necessary). In order to determine how much excess LDA was necessary, the excess CO_2 in the reactor was determined via titration. For this, an aliquot of 5 mL was taken out of the reactor and placed into a 25 mL round-bottom flask with a magnetic stir bar (prior heated and cooled under vacuum, then filled with argon). Fluorene as the indicator (ca. 5 mg) was added to the pale yellow solution, which was then titrated with the same batch *n*-BuLi solution, which was later used for the formation of LDA. A 0.36 mL amount was consumed until the color turned orange. The total amount of BuLi solution used in the next step therefore was 2.05 L (1 equiv) + 1.31 L (for quenching excess CO_2) + 0.672 L (20% safety margin) → total of 4.09 L (=2.78 kg). Diisopropylamine (1.027 L, 7.20 mol) was added to the reaction mixture at −57 °C. After 10 min *n*-BuLi solution (1.6 M in hexane, 4.09 L, 6.55 mol) was added during 30 min. After 15 min the reaction mixture was slowly warmed to −10 °C and stirred at −7 °C for 1.5 h. The reaction mixture was then quenched with 0.5 L of water during 15 min followed by the addition of 3.6 kg of $KHSO_4$ dissolved in 5 L of water (almost saturated solution). The pH dropped to 2−3. The reaction mixture was extracted with 1 × 5 L and 2 × 3 L of MTBE. The combined organic phases were washed twice with 3 L of brine, dried over sodium sulfate (with addition of 1.2 mL of Octastat 5000 as an anti-electrostatic agent), and filtered. The *cis*/*trans* ratio was determined to be 9:91 (as the benzyl esters). The brown, clear solution was concentrated to give 780 g of a brown solid with liquid parts in it.

Purification. The crude material was dissolved in 7 L of EtOAc at 70 °C. After being completely dissolved, half of the solvent was distilled off (crystallization already started) and replaced by 4 L of heptanes. This mixture was cooled to rt, then after 30 min to 0 °C. After another hour, the crystals were filtered off. The beige crystals were washed with 1 L of a cold EtOAc/heptanes (1:2) mixture, then dried for 6 h at 45 °C *in vacuo* to yield 420 g (crop 1). The *cis*/*trans* ratio was determined as 5:95. The mother liquor was concentrated, dissolved in 0.6 L of EtOAc, and diluted with 0.5 L of heptanes. An oil was formed, which did not crystallize even after addition of 0.4 g of seed crystals from the first crop. However, overnight crystals formed, which were filtered and washed. Then the 55 g (wet weight) was recrystallized from EtOAc/heptanes to yield 28.9 g of beige powder (crop 2). The *cis*/*trans* ratio was determined to be 8:92. Crops 1 and 2 were combined and recrystallized from 5.5 L of hot EtOAc (stirred at 70 °C); then 2 L was distilled off at 200 mbar. When the crystallization started, 1 L of heptanes was added and the suspension slowly cooled to rt overnight, while stirring. The suspension was stirred for 2 h at 5 °C and then filtered. The filter cake was washed with 1 L of ice cold EtOAc/heptanes, 2:1. The pale beige crystals were dried *in vacuo* at 45 °C for 3 h to yield 389 g (51%) of *rac-trans*-**30** with a *cis*/*trans* ratio of 1.6:98.4. Mp: 161−163 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.12 (br, 1H), 4.41 and 4.30 (2s, 1H, 2 rotamers), 3.63−3.50 (m, 2H), 1.78−1.67 (m, 1H), 1.58−1.52 (m, 1H), 1.45 and 1.41 (2s, 2 rotamers ca. 1:1, 9H), 0.81−0.76 (m, 1H), 0.38−0.30 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 176.7, 155.9, 154.8, 80.8, 80.5, 61.3, 61.0, 48.6, 48.3, 28.4, 28.3, 19.8, 18.6, 15.5, 14.9, 9.2, 9.0 (rotamers). HRMS (ESI): calcd for $C_{11}H_{16}NO_4$ $[M - H]^-$ 226.1079, found 226.1088. Anal. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.11; H, 7.32; N, 6.06.

Benzylation. All mother liquors were combined and evaporated to yield 301 g of a dark brown honey, which was dissolved in 3 L of acetone; then 456 g of potassium carbonate (3.3 mol) and 514 g of benzyl bromide (3 mol) were added, and the reaction mixture was stirred at rt overnight. Celite (300 g) was added, and the reaction mixture filtered. The solvent was removed *in vacuo* and replaced by 2.5 L of THF; then 1 L of 7 N ammonia in MeOH was added, and the reaction mixture stirred overnight. According to HPLC all excess BnBr was converted to benzylamine. The THF was distilled off, and 3 L of EtOAc and 3 L of water were added. After mixing, the phases were separated and the aqueous phase was extracted two more times with 1 L of EtOAc. The combined organic phases were washed twice with 2.5 L of 20% aqueous $KHSO_4$ aqueous solution. (After the first phase separation, some dark oil was removed with the water phase too; the pH of the water phase was <2.) The brown organic phase was washed with 2.5 L of brine, dried over sodium sulfate, concentrated, redissolved in 1 L of EtOAc/heptanes (1:1), filtered through a 5 cm thick plug of silica gel (diameter 11 cm), and rinsed with 3 L of EtOAc/heptanes (1:2). After removal of the solvent 321.6 g of a brown-orange oil was obtained . This material was purified on 2 kg of silica gel with EtOAc/heptanes in three portions. The first eluting fractions resulted in 72.7 g (6.5% yield) of *trans* benzyl ester *rac*-**36** with a purity of 93.5% at 215 nm. Later another 122.0 g of a yellow-orange, viscous oil eluted. According to HPLC, it contained 33% of the *cis*-benzyl ester *rac-cis*-**25** and 61% of dibenzyl ester **26**.

*Recycling of Diamine **27**.* The aqueous phase of the first reaction workup was filtered (ca. 1.5 L of wet solids were removed). To the filtrate were added 5 L of ice followed by 5 L of 30% aqueous NaOH solution. The milky mixture was extracted with 3 × 4 L of MTBE. The combined organic phases were washed with 3 L of brine, dried over sodium sulfate, and concentrated to yield 857 g of crude diamine as an orange-brown oil. After distillation at 0.1 mbar and 68−80 °C, 808 g of **27** was obtained as a clear liquid with a GC purity of 100% (93% recovery).

(+)-*trans*-(1*R*,2*R*,5*S*)-3-(*tert*-Butoxycarbonyl)-3-azabicyclo-[3.1.0]hexane-2-carboxylic Acid ((*R*)-*trans*-30) via Diastereomeric Salt Formation. *rac-trans*-**30** (180 g, 0.79 mol) and (*R*)-2-phenylglycinol (109 g, 0.79 mol) were placed in a 20 L evaporation flask of a Büchi Rotavapor R-220 and suspended in 10 L of EtOAc containing 0.5% water. The mixture was heated for 10 min at 70 °C, when a clear solution was obtained. The heating of the water bath was switched off, and the solution was allowed to cool to rt while gently stirring. After 6.5 h (internal temperature was 27 °C) the suspension was filtered off and the pale brown crystals dried under vacuum and recrystallized two more times at 70 °C in each 10 L of EtOAc to yield 109 g of the (*R*)-2-phenylglycinol salt as a colorless solid. Mp: 154.0−156.6 °C. Anal. Calcd for $C_{19}H_{28}N_2O_5$: C, 62.62; H, 7.74; N, 7.69. Found: C, 62.44; H, 7.54; N, 7.54. $[\alpha]^{23}_D$ = +54.8 (*c* 0.50, MeOH). This salt was treated with 2 L of cold 10% aqueous $KHSO_4$ solution and 1.5 L of EtOAc. The aqueous phase was extracted with 1 L of

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EtOAc. The combined organic phases were washed with 0.5 L of 10% aqueous $KHSO_4$ solution and twice with 1 L of brine, dried over magnesium sulfate, and concentrated to dryness. (*R*)-*trans*-**30** (53 g, 29% yield) as a colorless solid was obtained. Mp: 189−191 °C (dec). Enantiopurity (HPLC method 4, t_R = 7.06 min): >99% ee. ^{1}H NMR (600 MHz, DMSO-d_6): δ 4.09 and 4.05 (2s, 1H, 2 rotamers), 3.41−3.35 (m, ca. 2H, within H_2O signal), 1.62−1.54 (m, 2H), 1.37 and 1.32 (2s, 2 rotamers ca. 4:6, 9H), 0.74−0.70 (m, 1H), 0.23−0.17 (m, 1H). $[\alpha]^{24}_D$ = +122 (*c* 0.8, $CHCl_3$). The mother liquors were combined, and the enantio-enriched acid was liberated as described for the pure (+)-enantiomer; 104 g of a brown solid was obtained.

(−)-*trans*-(1*S*,2*S*,5*R*)-3-(*tert*-Butoxycarbonyl)-3-azabicyclo-[3.1.0]hexane-2-carboxylic acid ((*S*)-*trans*-30) via Diastereomeric Salt Formation. The 104 g of the above-described (−)-enantio-enriched acid plus 4 g of the same from a different batch (total 0.475 mol) and 65.2 g (0.475 mol) of (*S*)-2-phenylglycinol were placed in a 20 L evaporation flask of a Büchi Rotavapor R-220 and suspended in 8 L of EtOAc containing 0.5% water. The mixture was heated for 10 min at 70 °C, when a clear yellow solution was obtained. The heating of the water bath was switched off, and the solution was allowed to cool to rt while gently stirring. After the weekend (internal temperature was 21 °C) the suspension was filtered off and the pale brown crystals dried and recrystallized one more time at 70 °C in 8 L of EtOAc containing 0.5% water to yield 59 g of the (*S*)-2-phenylglycinol salt as a colorless solid. The salt was treated with 1 L of cold 10% aqueous $KHSO_4$ solution and 1 L of EtOAc. The aqueous phase was extracted with 0.5 L of EtOAc. The combined organic phases were washed with 0.3 L of 10% aqueous $KHSO_4$ solution and twice with 0.5 L of brine, dried over magnesium sulfate, and concentrated to dryness. (*S*)-*trans*-**30** (28 g, 15% yield based on 180 g of *rac*-*trans*-**30**) as a colorless solid was obtained. Mp: 187−190 °C (dec). Enantiopurity (HPLC method 4, t_R = 6.27 min): 95.6% ee. ^{1}H NMR (600 MHz, DMSO-d_6): δ 4.13 and 4.09 (2s, 1H, 2 rotamers ca. 2:3), 3.45−3.42 (m, ca. 2H, within H_2O signal), 1.66−1.58 (m, 2H), 1.41 and 1.36 (2s, 2 rotamers ca. 4:6, 9H), 0.78−0.74 (m, 1H), 0.26−0.21 (m, 1H). $[\alpha]^{23}_D$ = −121 (*c* 0.86, $CHCl_3$). **Via Hydrogenation of Benzyl Ester (*S*)-*trans*-25.** (*S*)-*trans*-**25** (5.0 g, 15.8 mmol) was dissolved in 80 mL of EtOAc, and 0.5 g of Pd/C 10% was added. The reaction mixture was hydrogenated for 9 h at rt and atmospheric pressure. The catalyst was filtered off and washed with MeOH, because product precipitated out. The solvent was removed, and the crude product crystallized from hot EtOAc. A 2.88 g amount of (*S*)-*trans*-**30** (80% yield) was obtained. Mp: 182−184 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.74 (br, 1H), 4.08 and 4.04 (2s, 2 rotamers, ratio 5:7, 1H), 3.43−3.35 (m, overlaid by H_2O signal, ca. 2H), 1.62−1.50 (m, 2H), 1.36 and 1.31 (2s, 2 rotamers ca. 4:5, 9H), 0.74−0.68 (m, 1H), 0.22−0.15 (m, 1H). $[\alpha]^{24}_D$ = −143.3 (*c* 0.51, $CHCl_3$).

***cis*-Benzyl 3-Azabicyclo[3.1.0]hexane-2-carboxylate (*rac*-*cis*-31).** To a solution of 2.13 g (6.7 mmol) of *rac*-*cis*-**25** in 23 mL of dichloromethane was added at rt 2.2 mL of TFA. The reaction mixture was stirred for 6 h; then saturated aqueous sodium bicarbonate solution was slowy added until the pH increased to >7. The organic phase was separated, and the aqueous phase extracted twice with dichloromethane. The combined organic phases were dried over sodium sulfate, filtered, and concentrated to yield 1.39 g (95%) of *rac*-*cis*-**31** as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38−7.30 (m, 5H), 5.17 (s, 2H), 3.74 (d, *J* = 3.7 Hz, 1H), 2.93 (d, *J* = 11.0 Hz, 1H), 2.76 (dd, *J* = 11.2, 3.4 Hz, 1H), 1.65−1.60 (m, 1H), 1.40−1.35 (m, 1H), 0.36−0.29 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.2, 136.5, 128.9, 128.5, 128.2, 66.2, 60.9, 48.8, 20.9, 18.0, 3.6. Purity (HPLC method 1, t_R = 3.17 min): 93.4%. HRMS (ESI): calcd for $C_{13}H_{16}NO_2$ $[M + H]^+$ 218.1181, found 218.1192.

***trans*-Benzyl 3-Azabicyclo[3.1.0]hexane-2-carboxylate (*rac*-*trans*-31).** The above procedure was followed starting with *rac*-*trans*-**25** except for the reaction time, which was 2 h. A 0.23 g (95%) amount was obtained as a yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.39−7.29 (m, 5H), 5.091, 5.104 (J_{AB} = 12.7 Hz, 2H), 3.06 (br, 1H), 2.93 (dd, *J* = 10.3, 3.4 Hz, 1H), 2.78 (d, *J* = 10.3 Hz, 1H), 1.52−1.47 (m, 1H), 1.40−1.34 (m, 1H), 0.47−0.42 (m, 1H), 0.31−0.28 (m, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.2, 136.8, 128.9, 128.4, 128.1, 65.7, 61.8, 48.3, 20.4, 16.9, 6.5. Purity (HPLC method 1, t_R = 3.11 min): 98.1%. HRMS (ESI): calcd for $C_{13}H_{16}NO_2$ $[M + H]^+$ 218.1181, found 218.1192.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra, crystallographic and computational data, additional experimental data for the enantioselective deprotonation, and data for a failed epimerization approach. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data (excluding structure factors) for the structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 798573 ((*R*)-phenylglycinol salt of (*R*)-*trans*-**30**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336 033 or e-mail: deposit@ccdc.cam.ac.uk].

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: markus.furegati@novartis.com.

Notes

The authors declare no competing financial interest.

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(29) In the salt screen the vial with EtOAc saturated with water did not show any crystal growth. On the other hand the vial with EtOAc gave only phenylglycinol salt in 56% yield with 74% ee. However, during the scale up we observed a breakdown of distereoselectivity, and we could not improve it by recrystallization from EtOAc. In some instances the mother liquor even showed a better ee than the crystals. The addition of a defined quantity of water (0.5%) solved the problem without having optimized this parameter.

(30) With the evidence that epimerization occurred during the benzylchloroformate experiments we were confident of finding conditions. For this transformation stoichiometric amounts of K_2CO_3, DIPEA, DBU, and BnMgCl in THF gave no conversion at 0 °C after 3 h. KOtBu, LiHMDS, KHMDS, LDA, and *sec*-BuLi (0.2 to 2.5 equiv) in THF at temperatures between −78 and 0 °C and reaction times of down to 1 min gave at best a *cis*/*trans* ratio of 11:89 accompanied by strong decomposition. Especially *rac*-*cis*-**25** seemed to be unstable under these conditions and decomposed to a great extent, releasing BnOH.

(31) 1 g of *rac*-*cis*-**25** was converted to *rac*-*trans*-**25** in 71% isolated yield. The *cis*/*trans* ratio in the crude mixture was 5:95.

(32) 12 g of (*R*)-*cis*-**25** were produced with 46% yield due to a temporary blockage of the tubing.

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