JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/jo4013282 • Publication Date (Web): 19 Aug 2013

Synthesis of all four stereoisomers of 3-(*tert*-butoxycarbonyl)-3-azabicyclo[3.1.0]hexane-2-carboxylic acid

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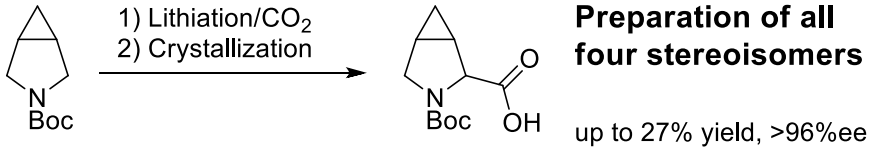


ABSTRACT

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

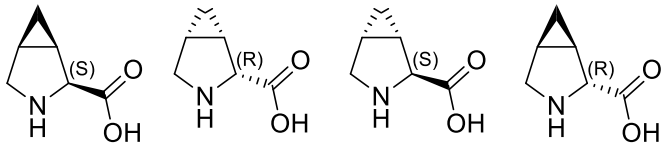
syntheses of these unnatural amino acids. With a simple adjustment of the reaction conditions, we were able to obtain either pure *cis* or *trans* acid. Optical resolution was accomplished via diastereomeric salt formation or alternatively via chromatography on a chiral stationary phase. Finally, *ab-initio* calculations gave an explanation for the observed *cis* selectivity in the initial step.

KEYWORDS

scale-up, lithiation, diastereomeric salt formation, flow, ab-initio.

INTRODUCTION

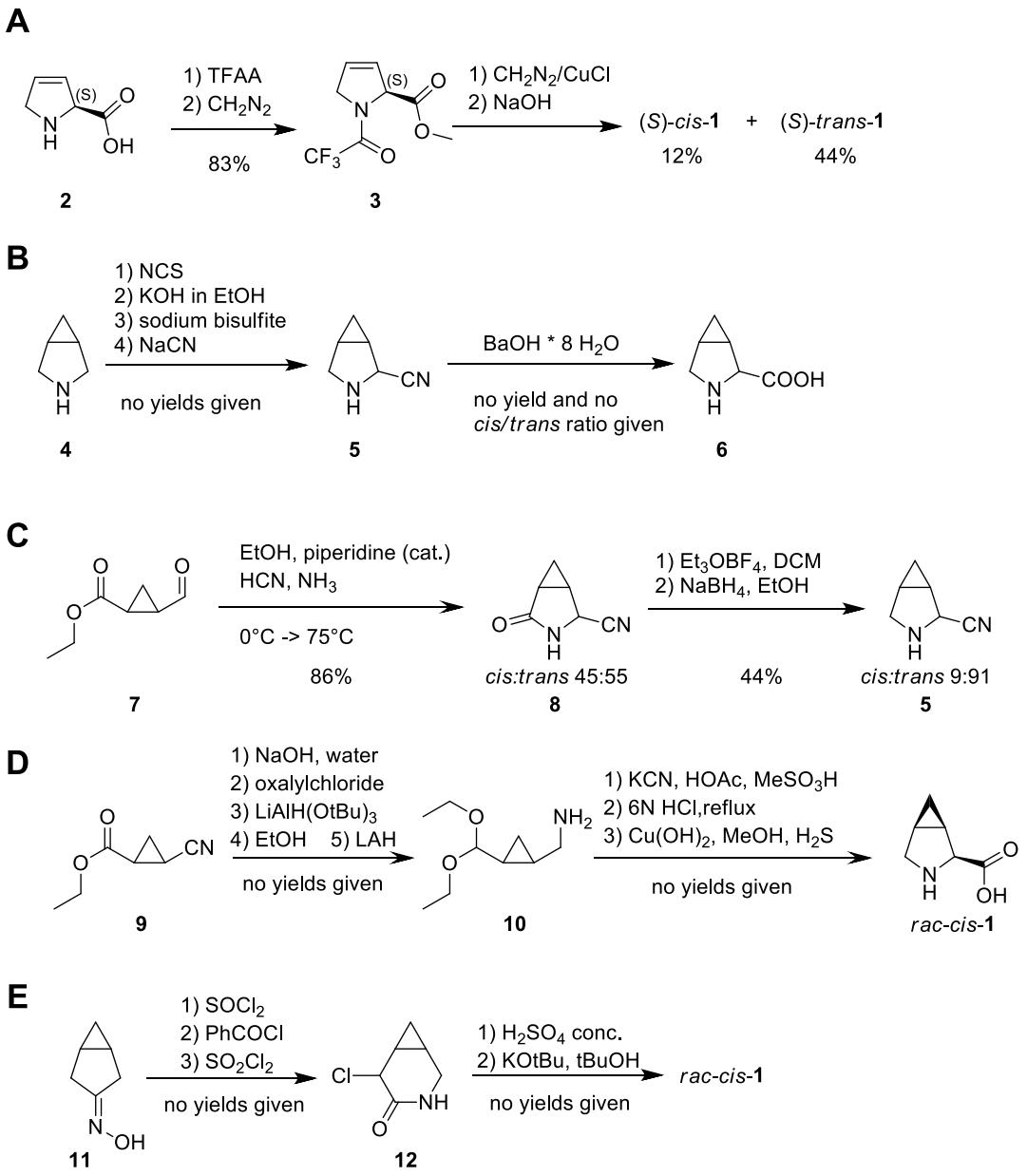
The four stereoisomers of 3-azabicyclo[3.1.0]hexane-2-carboxylic acid (series **1**), also referred to as 2-carboxy-3,4-methanopyrrolidines or 3,4-methanoprolines, belong to a unique class of amino acids.[1] The naturally occurring non-proteinogenic amino acid (*S*)-*cis*-**1** derived from L-proline 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]



(*S*)-*cis*-**1** (*R*)-*cis*-**1** (*S*)-*trans*-**1** (*R*)-*trans*-**1**

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 the geometric isomeric forms were 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]

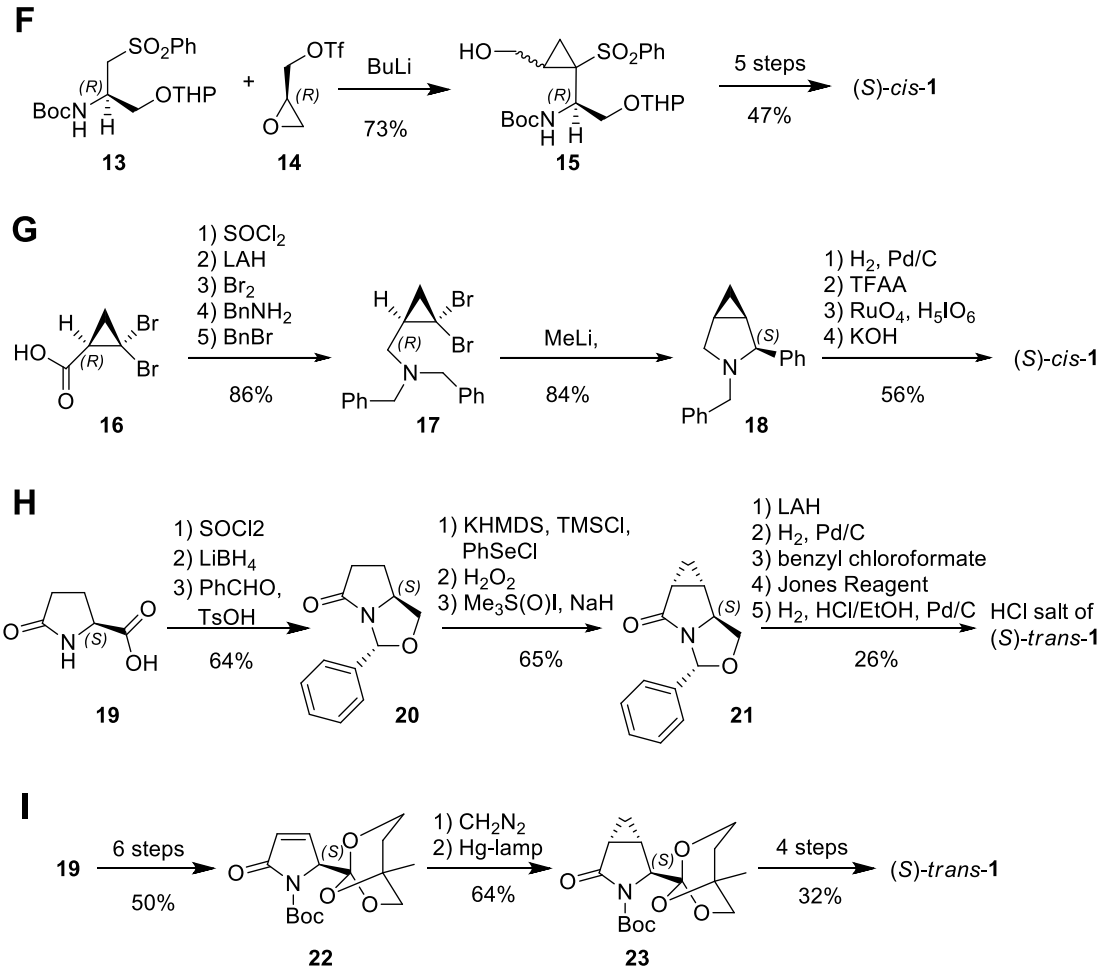
Scheme 1. Syntheses A-E of 3-azabicyclo[3.1.0]hexane-2-carboxylic acid



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 cyclising *cis*-1-ethoxycarbonyl-2-formylcyclopropane (**7**) with ammonia and hydrogencyanide 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-aminomethylcyclopropyl-1,2-diethylacetal (**10**) and ring closure to the pyrrolidine ring gave racemic (*S*)-*cis*-**1** in 8 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 3 steps (Scheme 1E).[11]

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



Starting with the chiral synthons **13** and (*R*)-glycidyl triflate (**14**), (*S*)-*cis*-**1** was obtained in 6 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 CH-bond adjacent to nitrogen as the key step to form bicyclo system **18** (Scheme 2G). The overall yield was 40%, however, starting material **16** had to be prepared via oxidation of 1,1-dibromo-2-vinylcyclopropane with $KMnO_4$ followed by resolution with dehydroabietylamine first.[13] The HCl salt of (*S*)-*trans*-**1** was prepared in 11 steps (11% overall yield) 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 towards (*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 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 kg quantities or can be prepared in 5 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%.

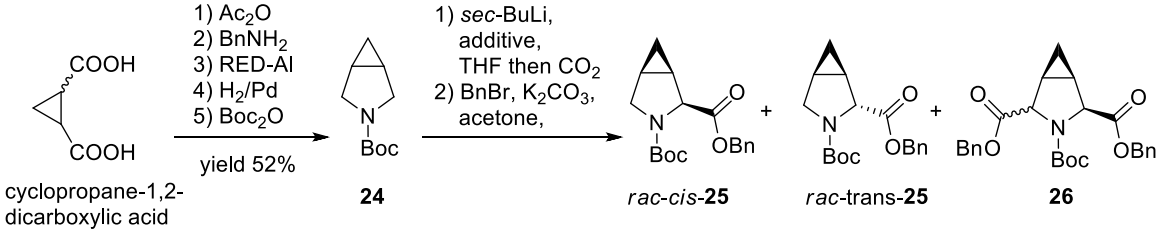
Lithiation of prolines and the use of diamine additives. Barker *et al*. showed that the diamine free lithiation of *tert*-butyl pyrrolidine-1-carboxylate (1.3 equiv. *sec*-BuLi in THF for 1 h at –40°C) and

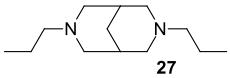
subsequent reaction with benzaldehyde gave 64% of the addition product.[17] In our hands, when these conditions were translated to the lithiation of substrate **24** followed by quenching with CO_2, neither the *cis*- nor the *trans*-acid was observed (Scheme 3 and Table 1 entry 1).[18]

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 diethylether 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]

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 *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.

Scheme 3. Literature synthesis of **24**, lithiation/CO_2 quenching and benzylation sequence



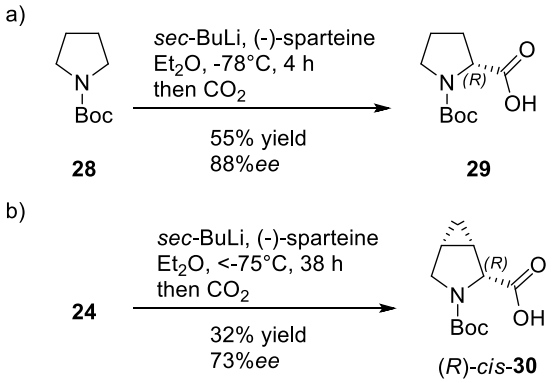
Entry	Additive	Reaction conditions	*rac-cis*-**25**	*rac-trans*-**25**	**26** [a]
1	none	5 h, –40°C	0	0	3
2	 **27**	5 h, –70°C	100 [b]	0	0
3	TMEDA	5 h, –70°C	77	2	21

[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 the quenching with CO_2.

Table 1. Results of the lithiation/CO_2 quenching step depending on the amine additive

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 than preparing the single enantiomers directly, we synthesised 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.

Scheme 4. Enantioselective deprotonation. a) literature, b) own work



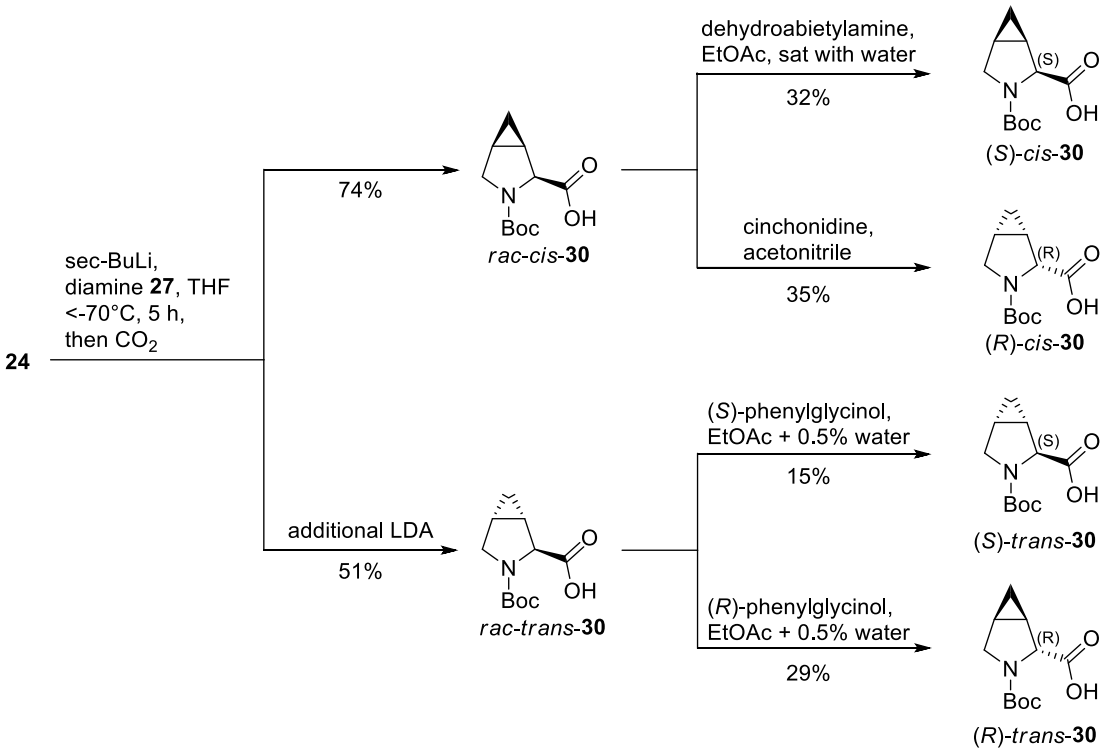
Approach 1 – Resolution by diastereomeric salt formation. Our first approach was to prepare *rac-cis*-**30** and *rac-trans*-**30** and resolve them via diastereomeric salt formation. The salt forming conditions

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 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** were prepared showing a 51% yield and containing less than 2% of the *cis* acid after two-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]

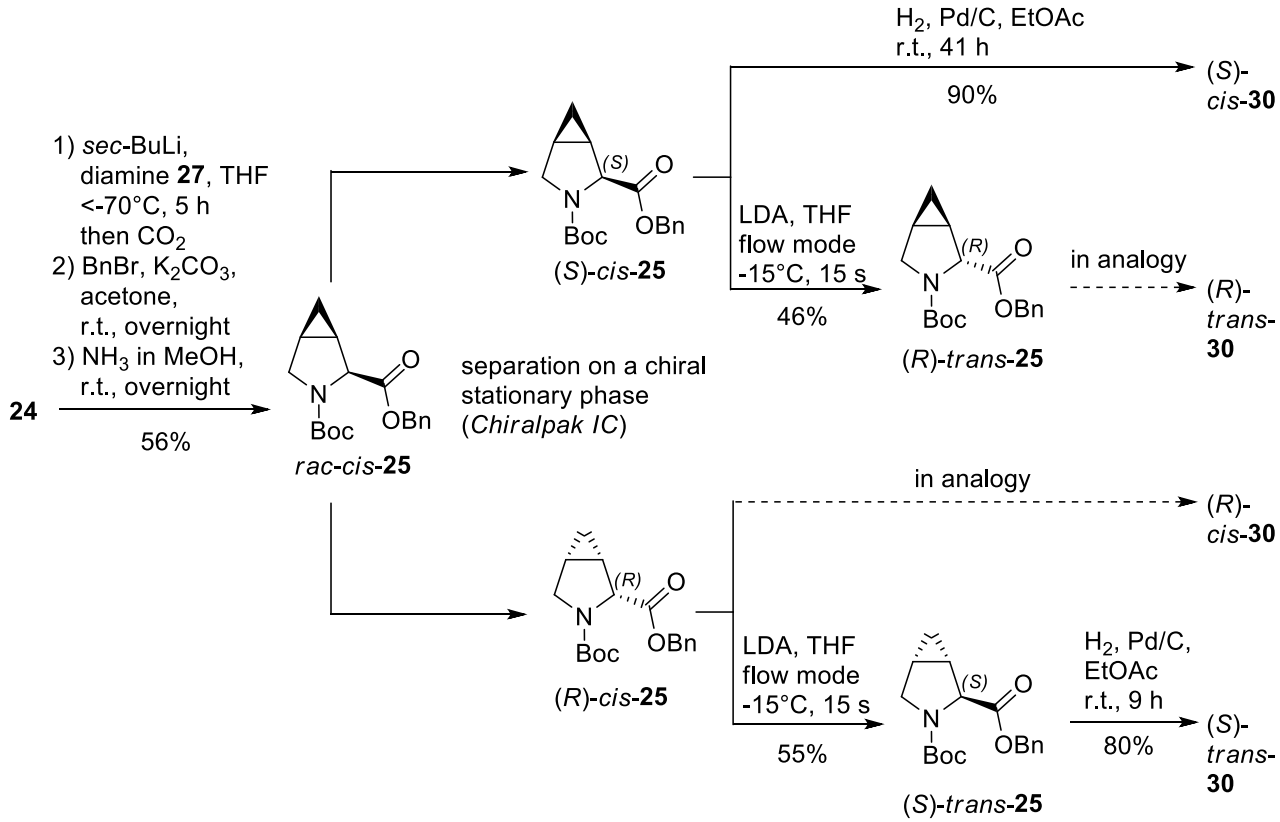
Scheme 5. Approach 1 – Resolution by diastereomeric salt formation



Approach 2 – Resolution by chromatography. From previous experiments we learned that it is possible to resolve benzylester *rac*-**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 benzylester 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 benzylester *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

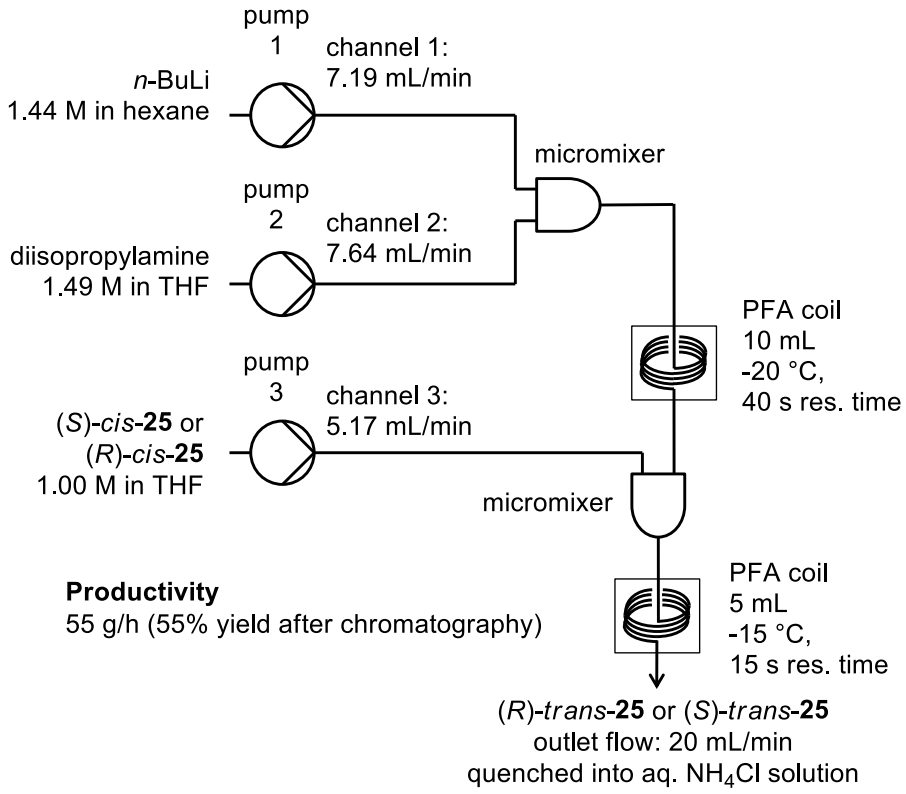
ammonia in methanol, the benzyl bromide was converted to benzylamine to facilitate removal by acid extraction. Chromatography on silica gel provided 242 g *rac-cis*-**25** in 58% yield. Next, we wanted to epimerize *rac-cis*-**25** to the *trans* ester *rac-trans*-**25**.

Scheme 6. Approach 2 – Resolution by chromatography



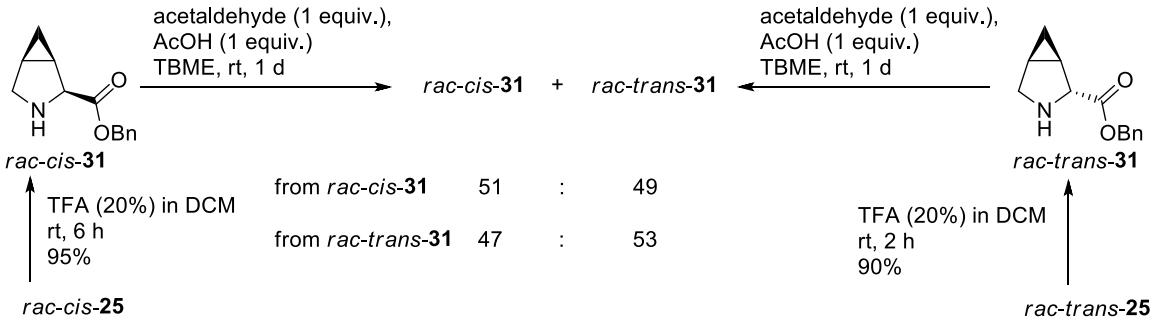
We identified LDA as the best base for the epimerization[30] and quickly learned that short reaction times were key to success. The short reaction time of <60 s necessary for batch reactions[31] would have been challenging for scaling up and we expected decreased yields for larger batches. With the aid 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.

Scheme 8: Aldehyde promoted epimerization via iminium intermediate



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, 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.

The 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 RMS = 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.

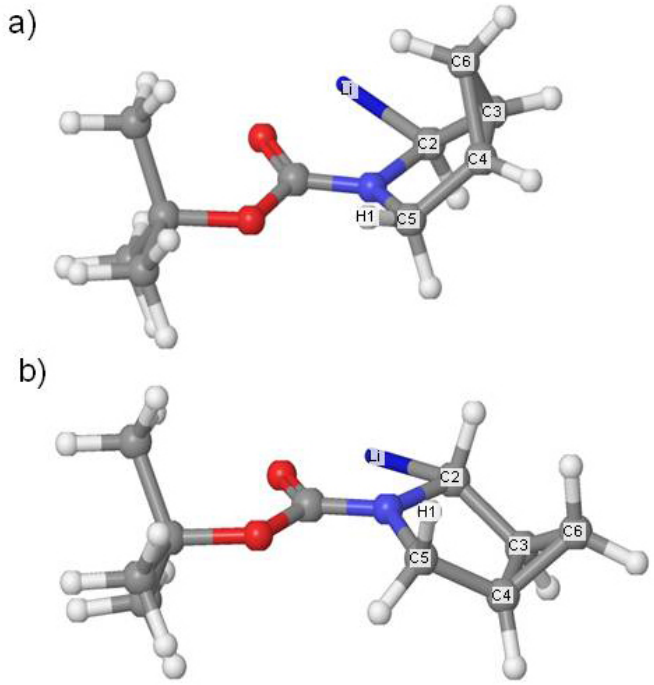


Figure 1: Energy minimized a) cis- and b) trans Li-complex of **24** (diamine **27** not shown for clarity) with atom naming convention used for describing dihedrals

In the overlay, both complexes are very similar, *i.e*. 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, the dihedral Li-C2-C3-C6 is 56.7º, the dihedral H-C2-C3-H is 48.9º, the dihedral H-C4-C5-H is 40.9º and the dihedral C6-C5-C4-H1 is 70.2º. For the minimum energy *trans*-structure, the dihedral Li-C2-C3-H is 16.9º, the dihedral H-C2-C3-C6 is 30.7º, the dihedral H-C4-C5-H is 8.4º 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 a resolution on a chiral stationary phase. Hydrogenation of these benzylesters 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. 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 x 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* determination): IC (IC00CE-LB014, 250x4.6 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 (250x4.6 mm, 5 um) column, hexane/2-PrOH 93:7 + 0.1% TFA, column temperature r.t., flow rate of 0.5 mL/min, detection at 210 nm, run time 40 min. HPLC method 4 (for *ee* determination): IC (250x4.6 mm, 5 um) column, heptanes/EtOH/MeOH 90:5:5 + 0.1% TFA, column temperature r.t., flow rate 1 mL/min, detection at 210 nm, run time 20 min. Purities were characterized with area% at the wave length declared for the method used. GC: Silaren column (30 m x 0.32 mm ID, 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 um 2.1 x 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 ISO 9001 standard. Glass vessels for small scale lithiation reactions were heated up to >150°C and cooled *in vacuo* or in a stream of argon. Specifications of the Vapourtec 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: Buechi 30 L hastelloy reactor (CR30) with FlexyALR Systag control. To a solution of 250 g (1.36 mol) *tert*-butyl 3-azabicyclo[3.1.0]hexane-3-carboxylate (**24**) and 360 g (1.71 mol, 1.25 equiv.) 3,7-dipropyl-3,7-diazabicyclo[3.3.1]nonane (**27**) in 5 L dry THF at –84°C were added within 15 min 1.46 L (2.05 mol, 1.5 equiv.) *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 was added 2 L of 20% $KHSO_4$ solution (until pH = 7) and 5 L water and warmed to ambient temperature. After 4 L THF were distilled off, the pH was lowered to 4 and the residue was extracted 3 times with a total of 7 L 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 acetone at r.t. to which were added 173 g (1.25 mol) potassium carbonate and

135 mL (1.14 mol) benzyl bromide. The reaction mixture was stirred at r.t. 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 heptanes for 1 h at r.t., filtered and concentrated to give 330 g 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 THF, then 320 mL of a 7*N* ammonia solution in MeOH were added and the reaction mixture stirred at 40°C for 6 h. The reaction mixture was concentrated and treated with 2 L 10% $KHSO_4$ solution, 1 L crushed ice and 2 L MTBE. The aqueous phase was extracted twice with each 0.8 L 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) *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 x 76 mm, 20 um; 100% dichloromethane; 270 mL/min at 25°C; detection at 250 nm. Analytical method: IC (IC00CE-LB014, 250 x 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). 104.0 g (51% recovery) of a colorless viscous oil were 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). 99.3 g (49% recovery) of a colorless viscous oil were 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 were 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) racemic *cis*-benzyl ester *rac-cis*-**25** in 15.4 mL 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 sat. aq, $NaHCO_3$ solution and warmed to r.t. 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 silica gel with

EtOAc/heptanes to yield 36 mg (3.7% yield) of the starting material and 0.69 g (71% yield) product *rac*-*trans*-**25** as a colorless viscous oil, that 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), 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 – 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 with 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 aq. 10% ice cold NH_4Cl solution. This was then extracted three times with 150 mL 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 benzylesters was 3:97. The crude product was purified on 2 kg 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 with 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) acid **30** or 0.5 mL of the reaction mixture (concentrated) were added 0.2 mL BnBr, 0.25 g potassium carbonate and 3 mL acetone. After stirring for at least 2 h at r.t. 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 4 necks and mechanical stirrer, internal thermometer and argon inlet. To a solution of 12 g (65.5 mmol) *tert*-butyl 3-azabicyclo[3.1.0]hexane-3-carboxylate (**24**) and 17.2 g (82 mmol, 1.25 equiv.) **27** in 262 mL dry THF, with the temperature kept below –60°C was added 56.1 mL (79 mmol, 1.2 equiv.) *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 aq. phase extracted twice with 150 mL MTBE. To the aq. phase ca 300 mL 25% aq. $KHSO_4$ solution and ice were added until the pH was < 3, then it was extracted three times with 200 mL MTBE. The combined organic

phases were washed with 200 mL brine, dried over sodium sulfate, filtered and concentrated. Some dichloromethane was added and the product completely dried on vacuum over night to yield 11.6 g *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 benzylesters). 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.) 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. Based on 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 4.0-3.2 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) *tert*-butyl 3-azabicyclo[3.1.0]hexane-3-carboxylate (**24**) in 19 mL dry THF at –40°C were added dropwise 2.53 mL (3.55 mmol, 1.3 equiv.) *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 h 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 r.t., when its consistency became jelly-like. The work up was identical as described for method A. 486 mg starting material were recovered from the basic extraction and 23 mg of a colorless resin were obtained after extraction at pH < 3 and benzylated for HPLC analysis. Neither *cis*- nor *trans* benzylester were detectable, the major signal corresponded to the bis-benzylated diester (**26**).

Salt screen. Resolution of racemic acids via formation of diastereomeric salts. *General procedure*. 192 combinations consisting of 16 chiral bases and 12 solvents were applied. For each combination 0.05 mmol 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-naphtylamine, 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 abs., MeOH, 2-PrOH, acetone, 2-butanone, EtOAc, EtOAc sat. 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 x 2 mL HPLC vials. After removal of the solvent the 12 different solvents were added and the vials closed with a 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 r.t. 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* 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 sat. 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) *rac-cis*-**30** in 20 L EtOAc (sat. with water) was added a solution of 164 g (0.52 mol) 90% pure (+)-dehydroabietylamine in 4 L EtOAc (sat. with water) at r.t. After the addition a precipitation formed. The suspension was heated to reflux for one hour. The clear solution was cooled to 20°C over 3 hours. A pale brown suspension was obtained that was stirred for another 3 hours. After filtration the filter cake was washed twice with 2 L cold EtOAc and dried 18 h at 10 mbar and 30°C. 86 g of the dehydroabietylamine salt were 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 dehydroabietylamine salt (combined with a trial batch) in 3 L deionized water were added 60 g

potassium carbonate and 3 L MTBE. After 5 min the two clear phases were separated. The aqueous phase was extracted twice with 1 L MTBE. The combined organic phases were extracted twice with 0.5 L water, dried over magnesium sulfate, filtered and concentrated to yield 70 g of a brown oil of recovered dehydroabietylamine. To the combined aq. phases, while vigorously stirred, were added 3 L EtOAc and 150 g citric acid. After 10 min the aq. phase was separated and extracted two more times with 1 L EtOAc. The combined organic phases were washed twice with 1 L water, dried over magnesium sulfate, filtered and concentrated at 45°C *in vacuo*. The resulting resin was triturated with low boiling petroleum ether for one hour 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 *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 that were suspended in 3 L of water. After the addition of 130 g potassium carbonate and 3 L MTBE, 75 g (+)-enantio enriched (*R*)-*cis*-**30** were isolated in analogy to the above procedure. **Via hydrogenation of benzylester (*S*)-*cis*-25.** (*S*)-*cis*-**25** (6.37 g, 17.7 mmol) was dissolved in 90 mL EtOAc and 0.94 g Pd/C 10% were added. The reaction mixture was hydrogenated for 41 h at r.t. and atmospheric pressure. The catalyst was filtered off and the product solution extracted with 150 mL sat. aq. $NaHCO_3$ solution. The aq. phase was extracted with another 100 mL EtOAc, then the pH was lowered by addition of citric acid and again extracted with 3 x 100 mL EtOAc. These three EtOAc portions were combined, washed with brine, dried over sodium sulfate and concentrated to yield 3.61 g (90% yield) (*S*)-*cis*-**30** as a colorless resin, that 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 acetonitrile were added 95 g (–)-cinchonidine. While heating to reflux, the suspension turned into a yellow solution. The oil bath was removed and the solution allowed to cool to r.t. After a few hours the crystals were filtered and washed with 0.5 L cold acetonitrile. The wet crystals were recrystallized in 1.3 L 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 deionized water and 63 g citric acid and then extracted with 6 L MTBE. The MTBE phase was washed twice with 2 L water. The combined aq. phases were extracted twice with 2 L 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 warm heptanes. After standing overnight at r.t., the crystals were filtered, washed twice with 100 mL cold heptanes and dried to yield 34.0 g 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 4 necks and mechanical stirrer, internal thermometer and argon inlet. 5.4 g (23.1 mmol, 1.25 equiv.) (–)-sparteine (distilled prior to use) were placed into the reaction flask and diluted with 230 mL dry diethylether. This 0.1 M solution was cooled below –70°C then 16.5 mL (23.06 mmol, 1.25 equiv.) of 1.4 M *sec*-BuLi solution in cyclohexane were added within 5 min. After being stirred for 15 min below –70° a solution of 3.38 g (18.45 mmol, 1 equiv.) 3-azabicyclo[3.1.0]hexane-3-carboxylic acid *tert*-butyl ester (**24**) in 15 mL diethylether were 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 r.t., then 25 mL of sat. aq. Na_2CO_3 solution were added and the two phases separated (another 70 mL water had to be added in order to dissolve precipitated salts). The aq. phase was extracted with 60 mL MTBE and the org. phase discarded. The pH of the aq. phase was set < 3 with 25% aq. $KHSO_4$ solution and then extracted three times with 60 mL MTBE. The combined org. phases were washed with brine, dried over sodium sulfate, filtered and concentrated to yield 1.53 g (37% yield) product as a colorless resin, that contained 11% of 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: Buechi 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 THF at –80°C was pumped *sec*-BuLi (1.4 M in cyclohexane, 2.88 L, 4.03 mol) within 45 min allowing the internal temperature not to exceed –75°C. After the complete addition the pump was purged with 0.5 L 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 methyl iodide. After 2 min this mixture was extracted with 10 mL MTBE and 2 mL water, 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, one hour 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°C 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, 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 stirrbar (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, that was later used for the formation of LDA. 0.36 mL were 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 water during 15 min followed by the addition of 3.6 kg $KHSO_4$ dissolved in 5 L water (almost saturated solution). The pH dropped to 2-3. The reaction mixture was extracted with 1 x 5 L and 2 x 3 L MTBE. The combined organic phases were washed twice with 3 L brine, dried over sodium sulfate (with addition of 1.2 mL Octastat 5000 as an anti electrostatic agent) and filtered. The *cis*/*trans* ratio was determined to be 9:91 (as the benzylesters). 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 EtOAc at 70°C. After being completely dissolved, half of the solvent was distilled off (crystallization already started) and replaced by 4 L heptanes. This mixture was cooled to r.t., then after 30 min to 0°C. After another hour, the crystals were filtered off. The beige crystals were washed with 1 L 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 EtOAc and diluted with 0.5 L heptanes. An oil was formed, that did not crystallize even after addition of 0.4 g seed crystals from the first crop. However, overnight

crystals formed, that were filtered and washed. Then the 55 g (wet weight) were recrystallized from EtOAc/heptanes to yield 28.9 g of beige powder (crop 2). *cis*/*trans* ratio was determined to be 8:92. Crop 1 and 2 were combined and recrystallized from 5.5 L hot EtOAc (stirred at 70°), then 2 L were distilled off at 200 mbar. When the crystallization started, 1 L heptanes was added and the suspension slowly cooled to r.t. overnight, while stirring. The suspension was stirred for 2 h at 5°C and then filtered. The filter cake was washed with 1 L 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 were dissolved in 3 L acetone, then 456 g potassium carbonate (3.3 mol) and 514 g benzyl bromide (3 mol) were added and the reaction mixture was stirred at r.t. overnight. Celite (300 g) was added and the reaction mixture filtered. The solvent was removed *in vacuo* and replaced by 2.5 L THF then 1 L 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 EtOAc and 3 L water were added. After mixing, the phases were separated and the aq. phase extracted two more times with 1 L EtOAc. The combined organic phases were washed twice with 2.5 L 20% aq. $KHSO_4$ aq. solution. (After the first phase separation, some dark oil was removed with the water phase too, pH of the water phase was < 2). The brown organic phase was washed with 2.5 L brine, dried over sodium sulfate, concentrated, re-dissolved in 1 L EtOAc/heptanes 1:1 and filtered through a 5 cm thick plug of silica gel (diameter 11 cm) and rinsed with 3 L 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 silica gel with

EtOAc/heptanes in 3 portions. The first eluting fractions resulted in 72.7 g (6.5% yield) *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 aq. phase of the first reaction work up was filtered (ca 1.5 L of wet solids were removed). To the filtrate were added 5 L ice followed by 5 L 30% aq. NaOH solution. The milky mixture was extracted with 3 x 4 L MTBE. The combined organic phases were washed with 3 L brine, dried over sodium sulfate and concentrated to yield 857 g crude diamine as an orange brown oil. After distillation at 0.1 mbar and 68-80°C, 808 g **27** were 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 Buechi Rotavapor R-220 and suspended in 10 L 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 r.t. 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 re-crystallized two more times at 70°C in each 10 L 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% aq. $KHSO_4$ solution and 1.5 L EtOAc. The aq. phase was extracted with 1 L EtOAc. The combined organic phases were washed with 0.5 L 10% aq. $KHSO_4$ solution, twice with 1 L 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 (decomp.). 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 liberated as described for the pure (+)-enantiomer, 104 g of a brown solid were 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) (*S*)-2-phenylglycinol were placed in a 20 L evaporation flask of a Buechi Rotavapor R-220 and suspended in 8 L 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 r.t. while gently stirring. After the weekend (internal temperature was 21°C) the suspension was filtered off and the pale brown crystals dried and re-crystallized one more time at 70°C in 8 L 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% aq. $KHSO_4$ solution and 1 L EtOAc. The aq. phase was extracted with 0.5 L EtOAc. The combined organic phases were washed with 0.3 L 10% aq. $KHSO_4$ solution, twice with 0.5 L brine, dried over magnesium sulfate and concentrated to dryness. (*S*)-*trans*-**30** (28 g, 15% yield based on 180 g *rac*-*trans*-**30**) as a colorless solid was obtained. Mp 187–190°C (decomp.). 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 benzylester (*S*)-*trans*-25.** (*S*)-*trans*-**25** (5.0 g, 15.8 mmol) was dissolved in 80 mL EtOAc and 0.5 g Pd/C 10% were added. The reaction mixture was hydrogenated for 9 h at r.t. 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. 2.88 g (*S*)-*trans*-**30** (80% yield) were obtained. Mp 182–184°C (decomp.). ^{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) *rac-cis*-**25** in 23 mL dichloromethane were added at r.t. 2.2 mL TFA. The reaction mixture was stirred for 6 h, then sat. aq. sodium bicarbonate solution was slowy added until the pH increased to > 7. The org. phase was separated and the aq. phase extracted twice with dichloromethane. The combined org. phases were dried over sodium sulfate, filtered and concentrated to yield 1.39 g (95%) *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** apart from the reaction time that was 2 h. 0.23 g (95%) were 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.

ACKNOWLEDGMENT

We thank Cara Brocklehurst for support and advice on the Vapourtec flow machine and for proof reading. Eric Francotte, Monique Kessler, for determining the optical purities and prep resolutions; Ina Dix for performing the X-ray analysis; Francis Roll for mass spectrometry and Monique Ponelle for NMR analyses.

ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H, ^{13}C NMR spectra, crystallographic and computational data, additional experimental data to the enantioselective deprotonation and data to a failed epimeriziation approach. This material is available free of charge via the Internet at http://pubs.acs.org.

Crystallographic Data. 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 email: deposit@ccdc.cam.ac.uk].

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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 only gave 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 the 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 eq.) in THF at temperatures between –78°C 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 (*R*)-*cis*-**25** were produced with 46% yield due to a temporary blockage of the tubing.

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