Evaluation of an aza-Michael approach for the synthesis of 3,3-dimethyl-2-aminocyclobutane-1-carboxylic acid

Florence Charnay-Pouget,[a] Michael Frank,[b] Jean-Pierre Baltaze,[a] Elisabeth Pereira,[b] and David J. Aitken[a],*

[a] Université Paris-Sud, ICMMO (UMR 8182-CNRS), 15 rue Georges Clemenceau, 91405 Orsay cedex, France
[b] Clermont Université, Université Blaise Pascal, Laboratoire SEESIB (UMR 6504-CNRS), 24 avenue des Landais, 63177 Aubière cedex, France
E-mail: david.aitken@u-psud.fr

This article is dedicated to Professor Ferenc Fülöp on the occasion of his 60th birthday

Abstract

The aza-Michael addition reaction of a dibenzylic amide anion with *t*-butyl 3,3-dimethylcyclobutene-1-carboxylate was investigated as a route to the title compound, a cyclic β-amino acid. In analogy with the known 5- and 6-membered ring homologues, the addition reaction proceeds smoothly, but with moderate diastereomeric and enantiomeric selectivities. The *trans* isomer of the title β-amino acid was obtained, for the first time, with a modest enantiomeric excess.

Keywords: Aza-Michael reaction, cyclobutenecarboxylate, β-amino acid, conjugate addition

Introduction

Alicyclic β-amino acids (β-AAs) are of importance as building blocks for the synthesis of diverse molecular structures, and as such are attractive targets for chemical synthesis.[1] In addition to their considerable pharmacological potential,[2] they play a key role in the construction of β-peptides which are designed to adopt well-defined secondary structures.[3] Oligomers of *trans*-2-aminocyclohexane-1-carboxylic acid (ACHC) have a tendency to adopt a 14-helical structure,[4] while the oligomers of *trans*-2-aminocyclopentane-1-carboxylic acid (ACPC)[5] or of *trans*-2-aminocyclobutane-1-carboxylic acid (ACBC)[6] fold into a 12-helix. Recent developments in this area show that the overall folding preference of a β-peptide is influenced not only by the identity of the cyclic β-AA which provides the backbone, but also the presence of substituents on

the peripheral parts of the alicycle. Thus, Fülöp and co-workers recently demonstrated that oligomers of a monoterpene-derived *trans*-β-AA, notionally a sterically challenged ACHC analog, preferred to adopt a 12-helix conformation in order to avoid long-range side-chain repulsions.[7]

In an effort to expand the set of available ring-substituted cyclic β-AAs, we envisaged the preparation of *trans*-3,3-dimethyl-2-aminocyclobutane-1-carboxylic acid **1** (Figure 1). This compound is a sterically-congested derivative of ACBC, but can also be viewed as a conformationally constrained analog of the β^2-AA 2-aminomethyl-4-methylpentanoic acid **2**, or of the β^3-AA β-homovaline **3**, both of which have been incorporated into designed β-peptide sequences.[8,9] Stereoselective routes to the parent ACBC have been established,[10] but their extensions to a non-symmetrical target such as **1** are not evident. The *gem*-dimethyl-ACBC core can be prepared via a thermal [2+2] cycloaddition reaction between an *N,N*-dialkylenamine derivative of isobutyraldehyde and an acrylate ester;[11] a major limitation is the imposition of a non-modifiable tertiary amine. Nonetheless, derivatives of **1** prepared in this way have been exploited periodically, notably as intermediates for the preparation of 3,3-dimethylcyclobutene-1-carboxylate esters.[12]
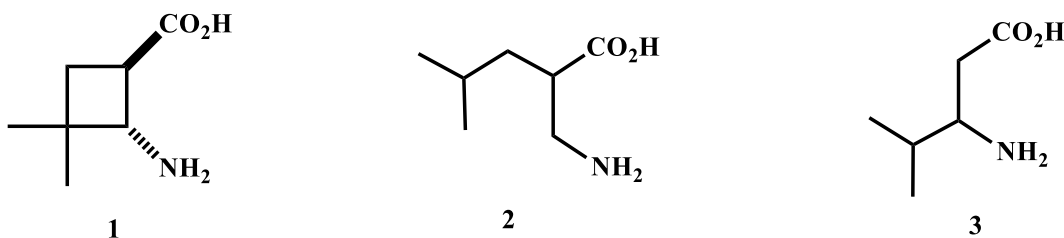

**Figure 1.** Structures of the target cyclobutane β-AA and related acyclic β-AAs.

We reasoned that a 3,3-dimethylcyclobutene-1-carboxylic ester might react in a conjugate addition manner with a nitrogen nucleophile which would be amenable to subsequent transformation into a primary amine. The aza-Michael reaction is a recognized general approach for the synthesis of β-AAs, and various asymmetric adaptations have been developped.[13] One of the most productive approaches, developed by Davies, has been the conjugate addition of enantiomerically pure lithium amides to unsaturated esters.[14] Indeed, asymmetric syntheses of *cis*-ACHC and *cis*-ACPC were described using this approach, and procedures for efficient epimerization were established, allowing access to *trans*-ACHC and *trans*-ACPC.[15] Extensions of the methodology have been described to allow enantioselective preparation of *cis* and *trans* isomers of 3- or 5-alkyl-ACPCs[16] and 6-alkyl-ACHCs,[17] as well as the pyrrolidine and tetrahydrofuran analogs of ACPC.[18] To date, however, the strategy has not been assessed as a route to smaller-ring β-AAs. We therefore studied the aza-Michael addition reaction as a route to the target molecule 3,3-dimethyl-ACBC.

Results and Discussion

Synthesis of the cyclobutene-1-carboxylic ester

Previous work on the conjugate addition of lithium amides advocates the use of *tert*-butyl esters as the Michael acceptors,[15,19] so our first task was to prepare *tert*-butyl 3,3-dimethylcyclobutene-1-carboxylate **4**. The corresponding methyl ester has previously been obtained by first preparing a methyl 2-dialkylaminocyclobutane-1-carboxylate via the thermal [2+2] cycloaddition reaction of methyl acrylate with an enamine obtained from isobutyraldehyde and dimethylamine,[11,12c,e] piperidine,[12b] or pyrrolidine,[12a,d] then conducting a Hofmann elimination on the adduct. We began our work adapting this process for the preparation of the *tert*-butyl ester **4**.

Enamine **5** was prepared from isobutyraldehyde and pyrrolidine[20] and was heating with *tert*-butyl acrylate in refluxing acetonitrile for 5 days. The requisite *tert*-butyl 2-pyrrolidinocyclobutane-1-carboxylate **6** was obtained in 91% yield (Scheme 1). NMR analysis of this compound suggested that the thermal [2+2] cycloaddition had been completely stereoselective, since only one diastereomeric form of **6** was present; the correlations observed in a 2D NOESY experiment indicated that it was the *trans* isomer (Figure 2). Since the corresponding *N,N*-dibenzyl derivative **8** was the anticipated product of the planned subsequent aza-Michael addition reactions (*vide infra*), we attempted its preparation using the thermal [2+2] reaction. In the event, heating *t*-butyl acrylate with the enamine **7**, obtained from *iso*-butyraldehyde and dibenzylamine,[11a] only gave a complex and intractable mixture of products (Scheme 1).
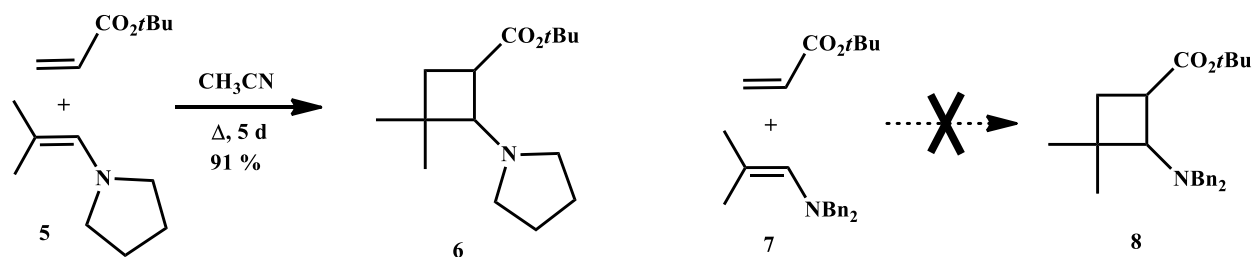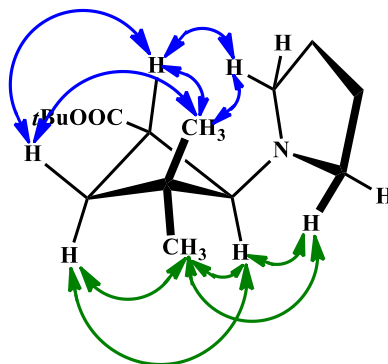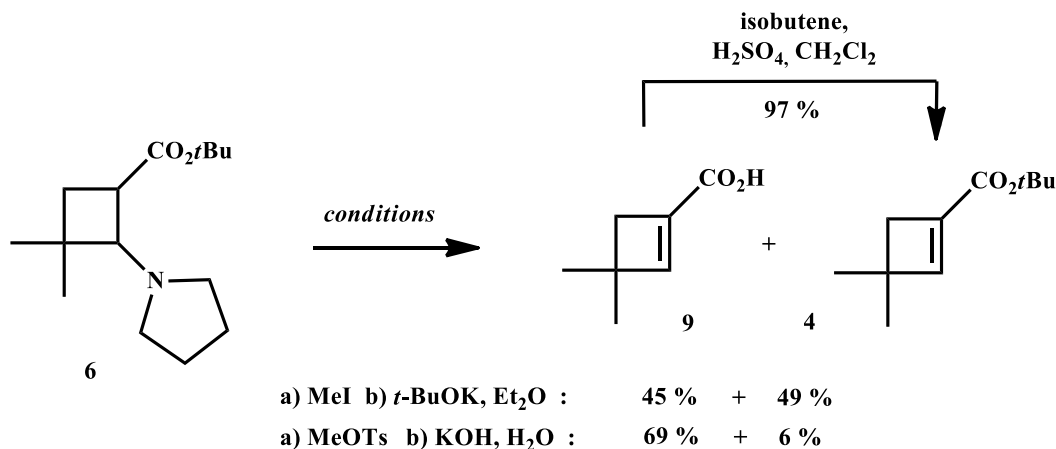
Scheme 1

Figure 2. 2D NOESY interactions observed for compound **6** (in CDCl$_3$).

Quaternization of the pyrrolidine adduct **6** with iodomethane followed by a potassium *tert*-butoxide-mediated Hofmann elimination gave the *tert*-butyl ester **4**, accompanied by the carboxylic acid **9**; this latter probably resulted from hydrolysis during the aqueous work-up. Indeed, using the original conditions (methyl tosylate then potassium hydroxide) from the literature work on the methyl ester,[11a] it was possible to obtain the acid **9** as the major product. In any event, re-esterification of the acid **9** could be achieved in high yield by treatment with *iso*-butene in anhydrous acidic conditions.

isobutene,
H_2SO_4, CH_2Cl_2

97 %

conditions

9   +   **4**

a) **MeI** b) *t*-**BuOK, Et$_2$O** :   45 %   +   49 %

a) **MeOTs** b) **KOH, H$_2$O** :   69 %   +   6 %

Scheme 2

Michael Addition reactions

The first series of experiments was conducted using a non-chiral lithium amide nucleophile derived from dibenzylamine (Scheme 3), in order to check the general feasibility of the Michael addition with acceptor **4** and to assess the diastereoselectivity of the reaction. Reactions were carried out by adding the nucleophile to a cold solution of **4** in THF, in analogy with Davies's procedures for the 5- and 6-membered ring homologues.[15] After 2 h reaction time, the mixture was quenched with a proton source and the products worked up by standard procedures. Yields and diastereomeric excess are presented in Table 1.

LiNBn$_2$

THF, 2 h,
then H$^+$

(see Table 1)

4   (±)-*cis*-**8**   +   (±)-*trans*-**8**

NaN(TMS)$_2$

t-BuOH
THF, 5 d
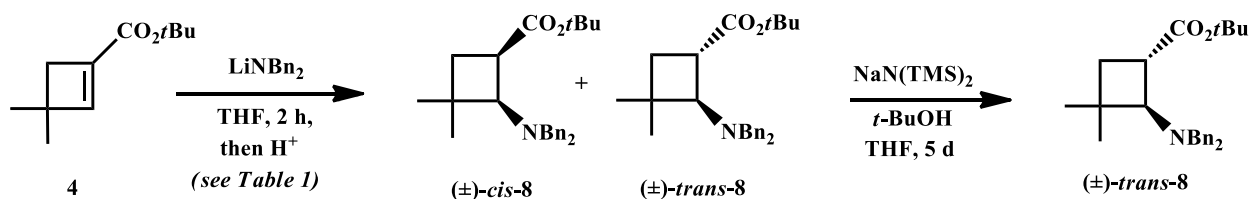
(±)-*trans*-**8**

Scheme 3

The general reaction profile was for the formation of a mixture of *cis* and *trans* isomers of adduct **8**, with the putative *cis* isomer dominating regardless of the proton source. The

diastereomeric ratio was estimated from the integration of the benzylic proton signals in the ^{1}H NMR spectra of the inseparable mixtures. Reaction mixtures held at –78 °C gave low-to-average yield of **8**, with low diastereomeric excess. When the mixture was warmed to –35 °C during the 2 h reaction period before quenching, both the yield of **8** and the diastereomeric excess improved, with the latter reaching 70%.

Table 1. Michael addition reactions of lithium dibenzylamide with unsaturated ester **4**

Reaction temperature (°C)	Proton source	Total yield of **8** (%)	Estimated ratio *cis:trans*
–78	NH$_4$Cl	32	50:50
–78	TFA	59	65:35
–78	2,6-di-*t*-butylphenol	62	60:40
–78 then –35	NH$_4$Cl	71	85:15
–78 then –35	TFA	80	80:20
–78 then –35	2,6-di-*t*-butylphenol	82	75:25

By analogy with Davies's work on 5- and 6-membered Michael acceptors,[15] the major component in samples of **8** was assumed to be the *cis* isomer. Davies's procedure for *cis*-to-*trans* isomerization was therefore applied to a 2:1 *cis/trans* mixture **8**. Treatment of this sample with sodium hexamethyldisilazide in THF for 5 days provided a sample of **8,** now composed of only the isomer for which the *trans* configuration had been assigned.

The second series of experiments was conducted using a chiral lithium amide nucleophile derived from (*S*)-(α-methylbenzyl)benzylamine (Scheme 4). In this case, the control of the configuration of the new stereogenic center at C2 of the adduct **10** is examined. Results are presented in Table 2.
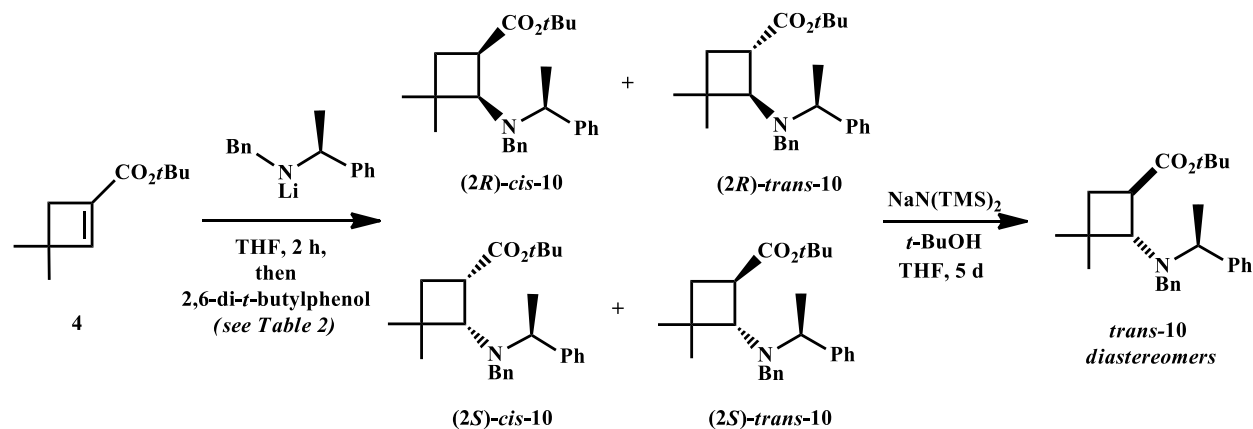
Scheme 4

Table 2. Michael addition reactions of chiral lithium amide with unsaturated ester **4**.

Reaction temperature (°C)	Total yield of **10** (%)	Estimated ratio (R)-cis:(R)-trans: (S)-cis:(S)-trans	Estimated ratio cis:trans	C2 stereoselectivity (R):(S)
–78 then –35	60	44:12:0:44	44:56	56:44
–78	72	50:31:0:19	50:50	81:19
–100 then –78	83	65:12:0:23	65:35	77:23

In three experiments, conducted at different temperatures, three of the four possible diastereomers of **10** were detected in the ^{1}H NMR spectra. It was not possible to identify the components stereochemically at this stage, but when one product mixture with a 65:23:12 diastereomer ratio was submitted to the *cis*-to-*trans* epimerization protocol, two of the three diastereoisomers were recovered, this time in a 0:74:26 ratio, respectively. We deduced that the major component of the three initially-formed isomers of **10** had a *cis* configuration, and that the epimerization procedure had converted it into the *trans* isomer with the same C2 absolute configuration. This observation suggested that the *cis*/*trans* selectivity profile for the reaction in Scheme 4 was poor, as had been the case in the achiral version (Scheme 3). More importantly, we were able to deduce the C2 stereoselectivity of the initial attack of the nucleophile. When the reaction mixture was allowed to warm to –35 °C after addition of the nucleophile, C2 stereoselectivity was very poor; however, keeping the reaction at –78 °C improved this situation somewhat to give a moderate stereochemical induction. Furthermore, the lower reaction temperature did not compromise the chemical yield of the β-amino ester. Davies had reported that the reaction of *t*-butyl cyclopentene-1-carboxylate with same chiral amide was conducted at –95 °C in order to achieve high C2 stereoselectivity;[15] in our case, the lower reaction temperature did not improve the moderate selectivity (nor the product yield).

The lack of control at C2 during the reaction in Scheme 4 can be rationalized in terms of steric hindrance. Davies showed that the preferred arrangement of conformation and stereofacial attack mode for chiral amides with cyclic and acyclic Michael acceptors corresponds to Figure 3.[21] In the case of a 3,3-dimethylcyclobutene-1-carboxylate substrate, such as **4**, interference from the C3 methyl groups could destabilize this mode of attack. In the event, given the low stereochemical excesses observed, it is not possible to assert whether this mode persists at all, nor whether other modes become prevalent.
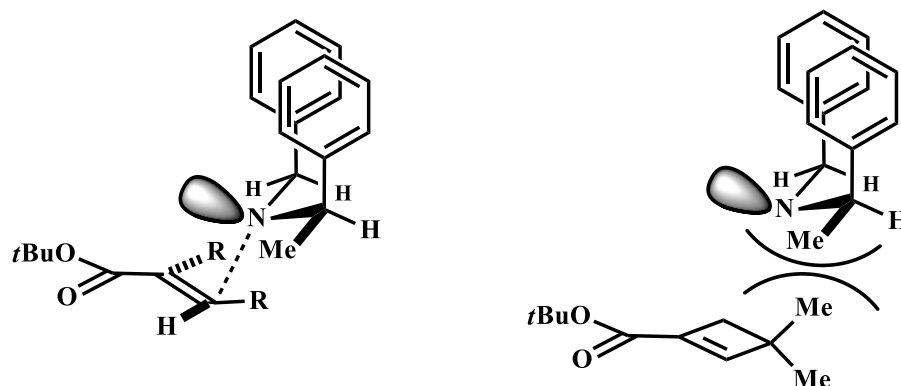
Figure 3. *Left*: Pictorial representation of the preferred approach of the amide nucleophile in its lowest energy conformation, leading to high C2 stereoselectivity. *Right*: Suggested steric repulsion which may disfavor this approach with the *gem*-3,3-dimethyl substrate **4**.

Access to the title compound

The first synthesis of the *trans* isomer of the title β-AA (**1**) was achieved (Scheme 5). The 3:1 mixture of the *trans*-**10** diastereomers obtained from the epimerization procedure was hydrogenated in the presence of Pearlman's catalyst then the ester group cleaved with TFA. After purification on a cation exchange column, the target molecule was obtained in near quantitative yield. The *trans* configuration of **1** was confirmed by a 1D nOe NMR experiment (Figure 4). It was gratifying to note that the amine deprotection could be carried out without loss of material, which has been problematic in the past due to a push-pull ring-opening reaction.[22] Indeed, we noted that a solution of *trans*-**1** in D$_2$O was stable for weeks at room temperature, whereas the corresponding ring-unsubstituted β-AA (*trans*-ACBC) visibly degrades in a few days in the same conditions. The enantiomeric excess (50%) of *trans*-**1**, determined by analytical reverse-phase hplc analysis on a chiral column, was in agreement with the diastereomeric composition of the precursor *trans*-**10**. Given the modest degree of enantioselectivity, the absolute configuration of the major enantiomer was not examined.
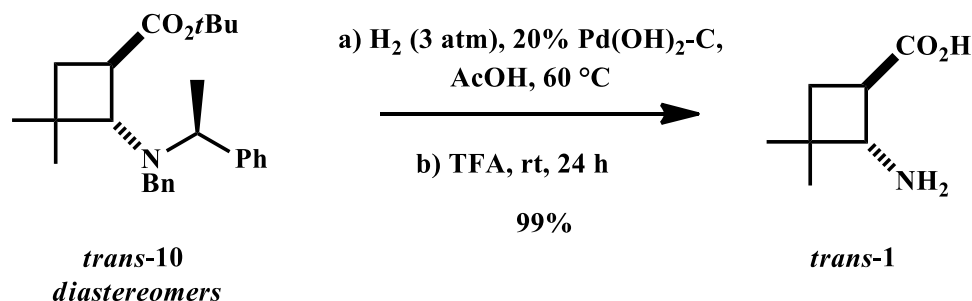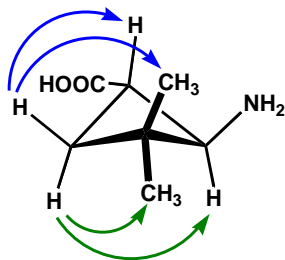

Scheme 5

Figure 4. 1D nOe enhancements observed upon irradiation of each of the C4 protons of compound **1** (in D_2O).

Conclusions

This work shows that the conjugate addition reaction of a lithium amide with an appropriate Michael acceptor is a valid synthetic approach for the preparation of the *trans* isomer of the title compound. In the racemic series the reaction proceeds with good, but not complete *cis* selectivity, while an efficient epimerization protocol provides entry to the *trans* isomer. Transfer of the methodology to the asymmetric synthesis series does not provide the high levels of C2 stereocontrol which have previously been reported for 5- and 6-membered ring substrates – it is possible that the presence of the *gem*-dimethyl substituents at C3 interferes with the usually preferred stereofacial approach.

Experimental Section

General. Solvents were dried and purified according to standard procedures. Flash chromatography was performed on columns of silica gel 60 (40-63 μm). Melting point ranges were taken on a Reichert microscope instrument. Optical rotation data were recorded on a Jasco DIP polarimeter. NMR spectra were recorded on a Bruker AC 400 instrument operating at 400 MHz (^{1}H) or 100 MHz (^{13}C). Chemical shifts δ are reported in ppm with respect to TMS, using residual solvent signals as internal references. ^{1}H signal multiplicity abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Low resolution mass spectra (MS) were obtained on a Hewlett-Packard HP 5989B instrument operating in chemical ionization (CI) mode using methane as the vector gas. High resolution mass spectra (HRMS) were obtained on a Bruker MicroTOFq instrument using positive-mode electrospray ionization (ESI).

***tert*-Butyl 2-*N*-pyrrolidino-3,3-dimethylcyclobutane-1-carboxylate (6).** Enamine **5** (14.1 g, 112.6 mmol) and *tert*-butyl acrylate (14.4 g, 112.6 mmol) were dissolved in acetonitrile (50 mL), and the mixture refluxed under argon for 5 days. After cooling, the solvent was removed on a rotary evaporator, then the residual oil was purified by flash chromatography (petroleum

ether/EtOAc, gradient from 80/20 to 0/100) to give the pyrrolidino ester **6** as a pale yellow oil (25.9 g, 91%). Bp 100-105 °C/0.5 mm. ^{1}H-NMR (CDCl$_3$): δ 0.90 (s, 3H, CH$_3$), 0.93 (s, 3H, CH$_3$), 1.24 (s, 9H, *t*Bu), 1.47-1.50 (m, 2H, CH$_2$), 1.52-1.55 (m, 4H, 2×CH$_2$), 2.15-2.25 (m, 4H, 2×CH$_2$), 2.35 (d, *J* = 8.6 Hz, 1H, CHN), 2.59 (q, *J* = 9.0 Hz, 1H, CHCO). ^{13}C-NMR (CDCl$_3$): δ 21.9 (CH$_3$), 22.9 (pyrrolidine CH$_2$), 27.7 (C(CH$_3$)$_3$), 29.3 (CH$_3$), 33.2 (C-4), 35.2 (C-3), 40.4 (C-1), 52.0 (pyrrolidine CH$_2$), 71.2 (C-2), 79.3 (OC(CH$_3$)$_3$), 173.7 (CO). HRMS (ESI): Calcd. for [C$_{15}$H$_{28}$NO$_2$+H]$^+$: 254.2115. Found 254.2114.

tert-Butyl 3,3-dimethylcyclobutene-1-carboxylate (4)
Method A. Hoffman elimination from pyrrolidino ester (6). A mixture of pyrrolidino ester **6** (500 mg; 1.97 mmol) and iodomethane (532 mg; 3.75 mmol) in acetonitrile (0.68 mL) was stirred at rt for 14 h. The mixture was concentrated *in vacuo* and the residue was dissolved in Et$_2$O (3.15 mL). A suspension of potassium *tert*-butoxide (662 mg; 5.91 mmol) in Et$_2$O (17 mL) was added, and the mixture was refluxed for 4 h. After cooling, 0.5 M HCl was added dropwise until pH = 1. The Et$_2$O layer was collected and the aqueous phase was washed with more Et$_2$O (2 × 5 mL). Combined organic phases were dried over MgSO$_4$ then the solvent was removed on a rotary evaporator to leave a yellow oil. Vacuum distillation (55-60 °C/1 mmHg) of this oil gave the desired *t*-butyl ester **4** (176 mg; 49%). The solid residue was identified as the known[11a] carboxylic acid **9** (111 mg; 45%).
Ester (4). Colorless oil. ^{1}H-NMR (CDCl$_3$): δ 1.14 (s, 6H, 2×CH$_3$), 1.48 (s, 9H, *t*Bu), 2.38 (s, 2H, CH$_2$), 6.72 (s, 1H, CH). ^{13}C-NMR (CDCl$_3$): δ 25.3 (2×CH$_3$), 27.7 (*t*Bu), 40.0 (C-3), 42.4 (C-4), 79.8 (C(CH$_3$)$_3$), 135.9 (C-1), 153.6 (C-2), 162.5 (C=O). HRMS (ESI): Calcd. for [C$_{11}$H$_{18}$NaO$_2$+Na]$^+$: 205.1199. Found 205.1194.
Acid **9**: white solid. Mp = 69-71 °C (pentane) (lit.[11a] 71.5-72.5 °C). ^{1}H-NMR (CDCl$_3$): δ 1.26 (s, 6H, CH$_3$), 2.44 (s, 2H, CH$_2$), 7.00 (s, 1H, H-2), 12.20 (br s, 1H, COOH). ^{13}C-NMR (CDCl$_3$): δ 25.3 (2×CH$_3$), 41.3 (C-3), 42.4 (C-4), 134.0 (C-1), 158.8 (C-2), 168.5 (C=O).
Method B. Esterification of carboxylic acid (9). Carboxylic acid **9** (4.79 g, 38 mmol) was dissolved in CH$_2$Cl$_2$ (40 mL) and the solution cooled to –78 °C. Isobutene (9 mL) was added by cannula, followed by sulphuric acid (0.3 mL). The mixture was stirred at –78 °C for 1 h then at –25 °C overnight. A saturated aqueous solution of NaHCO$_3$ was added until gas evolution stopped, then the organic phase was collected. The remaining aqueous solution was extracted with Et$_2$O (3 × 10 mL). Combined organic phases were washed with brine (2 × 10 mL) then dried over MgSO$_4$. The solvent was removed on a rotary evaporator, and the residue was purified by vacuum distillation as above to give the *t*-butyl ester **4** as a colorless oil (1.78 g, 97%).
Conjugate addition reaction of lithium *N,N*-dibenzylamide with ester (4)
A solution of *N,N*-dibenzylamine (3.2 mmol) in THF at 0 °C was treated with *n*-BuLi solution in hexane (3 mmol). The resulting red solution was cooled to the desired reaction temperature (-95 or –78 °C). A solution of ester **4** (1.0 mmol) in THF was added and the mixture was stirred for 2 h at the temperature indicated. The reaction was then quenched by addition of 2,6-di-*tert*-butylphenol (6 mmol) (or another proton source) then allowed to return to rt. The crude product

mixture was concentrated on a rotary evaporation, then partitioned between Et_2O and brine. The organic phase was dried over $MgSO_4$ and the solvent removed on a rotary evaporator. NMR analysis was performed at this stage in order to determine diastereomer ratios, then the crude product was purified by flash chromatography (cyclohexane/EtOAc, 50/1), to give an inseparable mixture of amino esters *cis*-**8** and *trans*-**8** (ratio approx. 3:1). Within this mixture, the following data are attributed to the major *cis*-**8** isomer: ^{1}H-NMR (CDCl3): δ 1.06 (s, 3H, CH3), 1.44 (s, 3H, CH3), 1.56 (s, 9H, *t*Bu), 1.73 (dd, *J* = 11.4 Hz, *J* = 4.4 Hz, 1H, CH2), 2.08 (dd, *J* = 11.4 Hz, *J* = 8.7 Hz, 1H, CH2), 3.25 (d, *J* = 9.1 Hz, 1H, H-1), 3.36 (td, *J* = 9.0 Hz, *J* = 3.9 Hz, 1H, H-2), 3.52 (d, *J* = 14.7 Hz, 2H, BnCH2), 3.79 (d, *J* = 14.7 Hz, 2H, BnCH2), 7.25-7.31 (m, 10H, ArH). ^{13}C-NMR (CDCl3): δ 22.5 (CH3), 28.1 (*t*Bu), 32.0 (CH3), 33.9 (CH2 cycle), 38.8 (C-3), 40.7 (C-1), 52.3 (NCH2), 65.8 (d, C-2), 80.3 (C(CH3)3), 126.7 (*p*-C), 128.0 (Ar-C-H), 129.3 (Ar-C-H), 137.7 (Ar-C), 174.1 (C=O).

***tert*-Butyl (±)-*trans*-2-(*N,N*-dibenzylamino)-3,3-dimethylcyclobutane-1-carboxylate (*trans*-8).**

A solution of *t*-BuOH (520 mg, 7.0 mmol) in THF (15 mL) was cooled to 0 °C and a solution of sodium hexamethyldisilazide in THF (2 M, 1.5 mL; 3.0 mmol) was added. This mixture was stirred for 15 min, then a solution of the **8** diastereomer mixture described above (301 mg, 0.8 mmol) in THF (5 mL) was added. The black solution was stirred for 5 days. The solvent was removed on a rotary evaporator, and the residue was partitioned between Et_2O and brine. The organic phase was dried over $MgSO_4$ and the solvent removed on a rotary evaporator to leave the crude product as a brown oil. NMR analysis was performed at this stage to establish that only one diastereomer was present (which had been the minor component in the starting sample). Purification by flash chromatography (cyclohexane/EtOAc, 50/1) furnished *trans*-**8** (242 mg, 80 %) as a paste-like solid. ^{1}H-NMR (CDCl3): δ 1.16 (s, 3H, CH3), 1.30 (s, 3H, CH3), 1.41 (s, 9H, *t*Bu), 1.53 (t, *J* = 10.2 Hz, 1H, CH2), 1.73 (t, *J* = 10.1 Hz, 1H, CH2), 2.76 (q, *J* = 9.5 Hz, 1H, H-1), 3.27 (d, *J* = 9.1 Hz, 1H, H-2), 3.48 (d, *J* = 14.3 Hz, 2H, BnCH2), 3.69 (d, *J* = 14.3 Hz, 2H, BnCH2), 7.20 (t, *J* = 7.2 Hz, 2H, Ar-H), 7.25-7.31 (m, 4H, ArH), 7.37 (d, *J* = 7.4 Hz, 4H, ArH). ^{13}C-NMR (CDCl3): δ 22.5 (CH3), 28.1 (*t*Bu), 30.3 (CH3), 34.1 (CH2 cycle), 36.9 (C-3), 40.2 (C-1), 56.0 (NCH2), 68.5 (C-2), 79.9 (C(CH3)3), 126.7 (*p*-C), 128.1 (Ar-C), 128.8 (Ar-C), 140.0 (*ipso*-C), 174.4 (C=O). MS (CI) *m/z* = 380 [M+H]$^+$. Anal. Calcd. for $C_{25}H_{33}NO_2$ (%): C, 79.10; H, 8.77; N, 3.69. Found: C, 79.01; H, 8.81; N, 3.62.

Conjugate addition reaction of lithium (*S*)-*N*-benzyl-*N*-α-methylbenzylamide with ester (4)

A solution of (*S*)-*N*-α-methylbenzyl-*N*-benzylamine (3.2 mmol) in THF at 0 °C was treated with *n*-BuLi solution in hexane (3 mmol). The resulting red solution was cooled to the desired reaction temperature (–95 or –78 °C). A solution of ester **4** (1.0 mmol) in THF was added and the mixture was stirred for 2 h at the temperature indicated. The reaction was then quenched by addition of 2,6-di-*tert*-butylphenol (6 mmol) (or another proton source) then allowed to return to rt. The crude product mixture was concentrated on a rotary evaporation, then partitioned between ether and brine. The organic phase was dried over $MgSO_4$ and the solvent removed on a rotary

evaporator. NMR analysis was performed at this stage in order to determine diastereomer ratios, then the crude product was purified by flash chromatography (cyclohexane/EtOAc, 50/1) to give an inseparable mixture of three diastereomers of amino ester **10**. The relative proportions were assessed from the benzylic signals in the ^{1}H-NMR spectrum (ratio approx. 3:1). Further interpretation or assignment of spectral data was not feasible.

tert-Butyl   _trans_-2-[(_S_)-_N_-α-methylbenzyl-_N_-benzylamino)]-3,3-dimethylcyclobutane-1-carboxylate (_trans_-10)

A solution of _t_-BuOH (2.22 g, 30 mmol) in THF (60 mL) was cooled to 0 °C and a solution of sodium hexamethyldisilazide in THF (2 M, 7 mL; 14 mmol) was added. The brown solution was stirred for 15 min then a solution of amino ester **10** (1.45 g, 3.7 mmol, as a 65:23:12 diastereomeric mixture) in THF (15 mL) was added. The black solution was stirred for 5 days. The solvent was removed on a rotary evaporator, and the residue was partitioned between Et$_2$O and brine. The organic phase was dried over MgSO$_4$ and the solvent removed on a rotary evaporator to leave the crude product as a brown oil (1.48 g). NMR analysis was performed at this stage to establish that only two diastereomers remained (those which had been the second and third most abundant in the starting sample). Purification by flash chromatography (cyclohexane/EtOAc, 50/1) furnished an inseparable mixture of two _trans_-**10** diastereomers (1.39 g, 96 %). Mp: 58-76 °C. MS (CI) _m/z_ = 394 [M+H]$^+$. Anal. Calcd. for C$_{26}$H$_{35}$NO$_2$ (%): C, 79.35; H: 8.96; N, 3.56. Found: C, 79.19; H, 8.88; N: 3.54.

The following data are attributed to the **major _trans_-10 isomer** in the mixture. ^{1}H-NMR (CDCl$_3$): δ 1.27 (s, 3H, CH$_3$), 1.39 (s, 3H, CH$_3$), 1.41 (s, 9H, _t_Bu), 1.42-1.60 (m, 4H, CH$_3$, CH$_2$), 1.74 (t, _J_ = 10.1 Hz, 1H, CH$_2$), 2.55 (q, _J_ = 9.4 Hz, 1H, H-1), 3.50 (d, _J_ = 15.0 Hz, 1H, CH$_2$), 3.61 (d, _J_ = 9.2 Hz, 1H, CHN), 3.69 (d, _J_ = 15.0 Hz, 1H, CH$_2$), 4.08 (q, _J_ = 6.7 Hz, 1H, C_H_CH$_3$), 7.15-7.40 (m, 8H, ArH), 7.63 (d, _J_ = 7.7 Hz, 2H, ArH). ^{13}C-NMR (CDCl$_3$): δ 9.7 (CH$_3$), 22.5 (CH$_3$), 28.1 (C(CH$_3$)$_3$), 30.1 (CH$_3$), 35.1 (CH$_2$), 36.7 (C(CH$_3$)$_2$), 40.2 (C-1), 50.8 (CHN), 56.3 (NCH$_2$), 65.3 (C-2), 79.6 (C(CH$_3$)$_3$), 126.2, 126.2, 126.6, 126.6, 126.9, 127.4, 127.6, 127.7, 127.9, 127.1, 128.2, 128.3, 128.7, (Ar-CH, overlapping with minor isomer signals), 142.0 (Ar-C), 143.8 (Ar-C), 174 2 (C=O).

The following data are attributed to the **minor _trans_-10 isomer** in the mixture. ^{1}H-NMR (CDCl$_3$): δ 0.88 (s, 3H, CH$_3$), 1.23 (s, 3H, CH$_3$), 1.38 (s, 9H, _t_Bu), 2.97 (q, _J_ = 9.4 Hz, 1H, H-1), 3.38 (d, _J_ = 9.3 Hz, 1H, CHN), 3.78 (d, _J_ = 13.8 Hz, 1H, CNCH$_2$), 3.85 (d, _J_ = 12.7 Hz, 1H, NCH$_2$), 3.99 (q, _J_ = 6.9 Hz, 1H, C_H_CH$_3$), other signals masked. ^{13}C-NMR (CDCl$_3$): δ 15.0 (CH$_3$), 22.6 (CH$_3$), 28.2 (C(CH$_3$)$_3$), 29.5 (CH$_3$), 33.2 (CH$_2$), 38.7 (C(CH$_3$)$_2$), 41.0 (C-1), 51.7 (CHN), 56.2 (NCH$_2$), 141.9 (Ar-C), 143.1 (Ar-C), other signals masked.

trans-2-Amino-3,3-dimethylcyclobutane-1-carboxylic acid (_trans_-1)

A mixture of diastereomers of amino ester _trans_-**10** (190 mg, 0.48 mmol, dr ~3:1) was dissolved in glacial acetic acid (25 mL) and a spatula tip of Pd(OH)$_2$-C was added. The mixture was Parr hydrogenated (3 atm) at 60 °C for 20 h. The mixture was cooled and filtered through Celite, with the solid residue being washed through with MeOH. The solvents were removed on a rotary

evaporator. The residue was partitioned between CH_2Cl_2 and a saturated aqueous solution of $NaHCO_3$. The organic phase was collected, dried over $MgSO_4$, then the solvent was removed on a rotary evaporator to leave a mixture of a yellow oil and some solid material (126 mg). To this residue was added TFA (4 mL), and the resulting solution was stirred at rt for 24 h. The solvent was removed on a rotary evaporator, and the residue was treated with ethereal HCl and MeOH, then evaporated to dryness on a rotary evaporator. The residue was partitioned between 0.5 M HCl (5 mL) and Et_2O (5 mL). The aqueous phase was collected and reduced to a volume of 2 mL, then applied to a column of H^+ ion exchange resin (Dowex 50X8 20-50 mesh). After elution with 1 M NH_4OH, and evaporation of appropriate fractions, the product was obtained as a sticky solid, which was washed once with ether to give the title β-AA *trans*-**1** (70 mg, 99 %). Mp: 153-157 °C. $[\alpha]_D^{20}$ +23.7 (*c* 0.54, H_2O). ^{1}H-NMR (D_2O): δ 0.94 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.54 (t, *J* = 10.3 Hz, 1H, CH_2), 1.84 (t, *J* = 10.7 Hz, 1H, CH_2), 2.85 (q, *J* = 9.5 Hz, 1H, CHCO), 3.39 (d, *J* = 8.6 Hz, 1H, CHN). ^{13}C-NMR (D_2O): δ 23.2 (CH_3), 30.1 (CH_3), 30.4 ($\underline{C}(CH_3)_2$), 37.1 (CH_2), 43.4 (CH), 58.1 (CH), 183.3 (C=O). HRMS (ESI): Calcd. for $[C_7H_{13}NO_2+H]^+$: 144.1025. Found: 144.1024.

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