DOI: 10.1002/ejoc.200900882

Enantiomerically Pure Cyclopropylamines from Cyclopropylboronic Esters

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Keywords: Cyclopropane / Boron / Asymmetric synthesis / Amines / Natural products

Cyclopropylamines are versatile intermediates and products both in organic synthesis in general and for active substances in particular. Although the synthesis of the corresponding enantiomerically pure cyclopropylboronic esters had been established previously, the C–B to C–N transformation was elusive. A detailed study directed towards the synthesis of several enantiomerically pure cyclopropylamines is disclosed; tranylcypromine [(1*S*,2*R*)-**36**] and the known belactosin A intermediate **43** were both obtained by use of trifluoroborates as key intermediates.

Introduction

The importance of cyclopropanes as synthetic intermediates, as well as the occurrence of the substructure in physiologically active natural products,[1] is well documented, and an impressive number of synthetic methods directed towards this motif have consequently been reported.[2] Furthermore, aminocyclopropanes in particular are incorporated in a number of drugs such as tranylcypromine[3] and trovafloxacin[4] or in aminocyclopropanecarboxylic acids,[5] but also as key elements in natural products such as coronatine[6] or belactosin A (Figure 1).[7] A number of syntheses have been disclosed, including the cyclopropanation of enamines and aminonitriles,[8] the amidocyclopropanation of alkenes,[9] the Curtius rearrangement,[10] the reductive amination of cyclopropanone acetals[11] or the reduction of nitrocyclopropanes,[12] although not every method has been widely applied. For enantiomerically pure products – essential for drug synthesis – a number of approaches have been successfully applied,[13] one of the most prominent recent examples being the de Meijere[14] variation of the Kulinkovich[15] hydroxycyclopropanation.

Our own synthetic efforts are based on the utilisation of enantiomerically pure and highly stable cyclopropylboronic esters (Figure 2).[16] We envisaged two alternative approaches towards cyclopropylamines **1**: The first approach was a Curtius sequence in the presence of a boronic ester leading to intermediate **2**, followed by conversion of the boron functionality. In a second alternative we utilised the boronic ester **3** in a C–B to C–N conversion. It should be noted that methods and reagents commonly used for

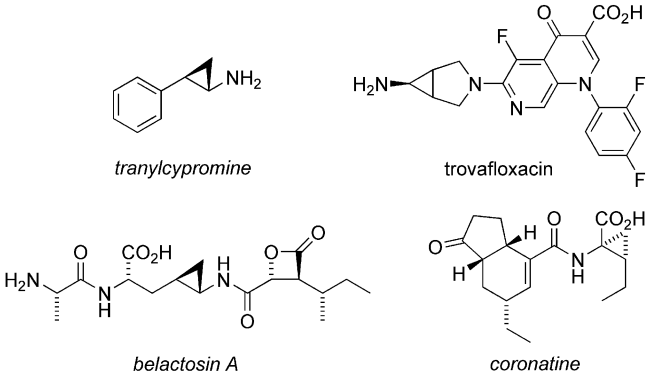

Figure 1. Selected physiologically active aminocyclopropanes.

aminations do not affect boronic acids or esters, but tend to require the intermediacy of more electrophilic boron substrates such as trialkylboranes, borinic acids or dichloroboranes.[17] However, our recent progress with the corresponding trifluoroborates[18] encouraged us to pursue the strategy. We had previously demonstrated that cyclo-

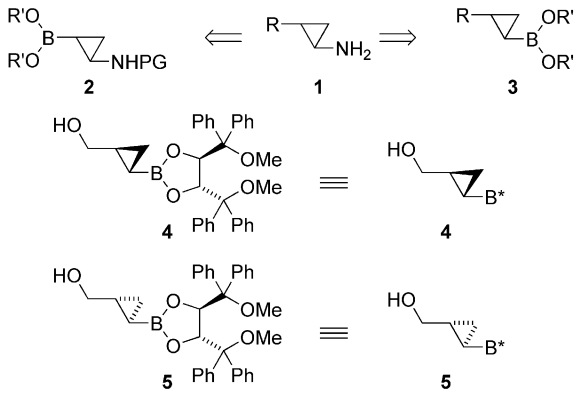

Figure 2. Cyclopropylamines from cyclopropylboronic esters **4** and **5**.

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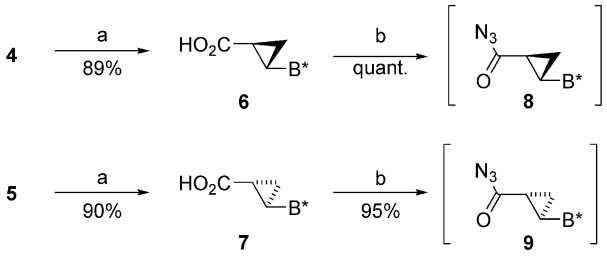
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900882.

propylboronic esters **4** and **5**[19] could indeed be utilised for both routes;[20] here we describe the full details of our findings.

Results and Discussion

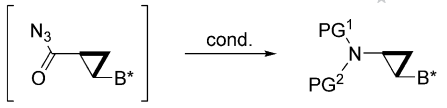
Cyclopropylamines by Curtius Rearrangement

The substrates for the Curtius rearrangement were readily synthesised by a two-step sequence starting from the primary alcohols **4** or its diastereomer **5** (Scheme 1). Oxidation provided the corresponding carboxylic acids **6** (89%) and **7** (90%), respectively. The acyl azides **8** and **9** were obtained in high yield (quant./95%) after mixed anhydride activation followed by treatment with sodium azide.



Scheme 1. Conditions: (a) $NaIO_4$ (3 equiv.), $RuCl_3{\cdot}H_2O$ (5%), $CCl_4/CH_3CN/H_2O$, room temp., 15 h; (b) (i) Et_3N (1.5 equiv.), $ClCO_2Et$ (1.5 equiv.), THF, 0 °C, 30 min, (ii) NaN_3 (50 equiv.), 0 °C, 30 min.

We next investigated Curtius rearrangements of the acyl azides, directly introducing different protecting groups at the amine moiety. When starting from azide **8**, heating in toluene (100 °C) in the presence of benzyl alcohol furnished the carbamate **10a** in high yield (Scheme 2, Entry 1). To establish a route towards the phthalimide-protected aminocyclopropylboronate **10b**, the free amine was trapped with phthalic anhydride after neutralisation of the reaction mixture with triethylamine (Entry 2). It should be noted that the isolation of free amine proved difficult and was consequently omitted. The product **10b** was obtained in moderate yield (67%) after column chromatography, but the crude product (obtained in 92% yield) could also be directly used for further transformations. When isocyanate formation in the presence of *tert*-butyl alcohol was examined, more equivalents of the nucleophile were found to be needed. The best results for the carbamate **10c** (Entry 3, 84%) were obtained in neat alcohol; the yield was significantly lower when only 6 equiv. were used (39%). This was obviously not a problem with the diastereomer **9**, and hence the benzylcarbamate **10d** was again obtained in high yield (90%, Entry 4) under standard conditions (1 equiv. BnOH, toluene, 100 °C, 4 h). In a last experiment, we formed the corresponding free amine from azide **9** and treated it directly with anisaldehyde under Dean–Stark conditions; after workup, the crude imine was reduced with $NaBH_4$ to give the PMB-protected (PMB: *p*-methoxybenzyl) aminocyclopropane **10e** in 66% yield over three steps (Entry 5).

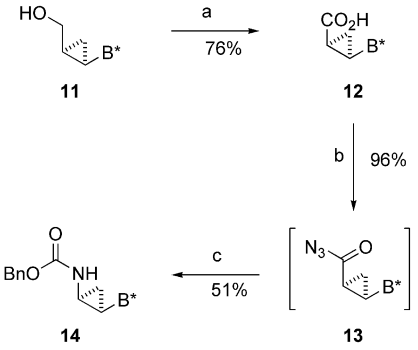


Entry	Substrate	Conditions	Yield	Product
1	**8**	1.0 equiv. BnOH, toluene, 100 °C, 4 h	90%	**10a**
2	**8**	*i* toluene, 100 °C, 30 min; *ii* 1.2 equiv. HCl 37%, 2 h; *iii* Et_3N, pH > 7; *iv* 5.7 equiv. phthalic anhydride, 70 °C, 12 h	67%	**10b**
3	**9**	55 equiv. *t*BuOH, 90 °C, 2 d	84%	**10c**
4	**9**	1.0 equiv. BnOH, toluene, 100 °C, 4 h	90%	**10d**
5	**9**	a) *i* toluene, 100 °C, 2 h; *ii* 1.3 equiv. HCl 37%, 30 min; *iii* 1.3 equiv. anisaldehyde reflux, 15 h; b) 2 equiv. $NaBH_4$, $MeOH/Et_2O$ –20 °C, 40 min	66%	**10e**

Scheme 2. Curtius rearrangements of acyl azides **8** and **9**.

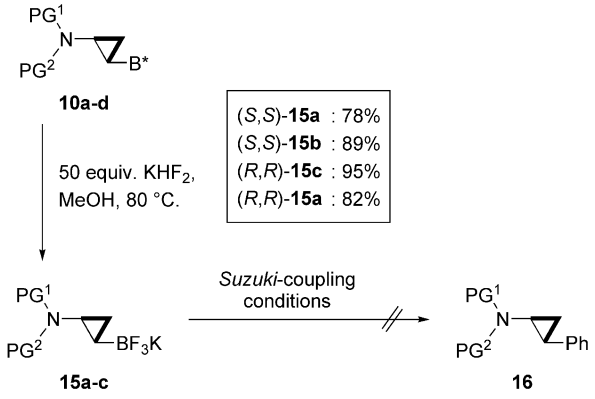
The same route was also tested for the *cis* series, starting from the diastereoisomerically pure alcohol **11**.[16c] Oxidation to the acid **12** and formation of the acyl azide **13** was straightforward, furnishing the intermediates in 76% and 96% yields, respectively (Scheme 3). However, it should be noted that the formation of the acid **12** was somewhat sluggish and the intermediate aldehyde more stable than expected. Furthermore, the acid **12** decomposed upon treatment with acetic acid, addition of which to the mobile phase during chromatographic purification consequently had to be omitted. Curtius rearrangement with water as nucleophile did not lead to the desired product; neither the intermediate nor the trapped product could be detected. Only the more reactive benzyl alcohol would react with the isocyanate, forming the desired benzylcarbamate **14** in moderate yield (51%). These findings are in good agreement with previous observations for *cis*-substituted compounds and might be due to the proximity of the nucleophile to the boron group.

In order to take advantage of the potential transformations on the boron moiety, the esters **10a–d** had to be converted into more active species. The method of choice was our previously established conversion into the corresponding trifluoroborates **15**.[18] Under the reported conditions [KHF_2 (50 equiv.), MeOH, 80 °C] products **15a–c** were all obtained in good to excellent yields (Scheme 4, 78–95%; PG = protecting group). However, all attempts to convert



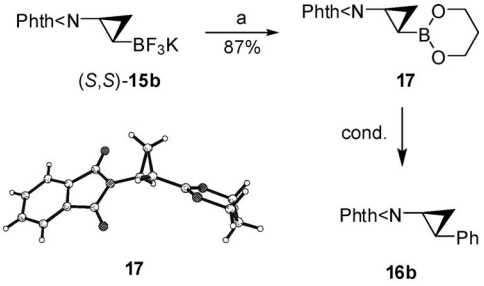
Scheme 3. Conditions: (a) $NaIO_4$ (3 equiv.), $RuCl_3 \cdot H_2O$ (5%), $CCl_4/CH_3CN/H_2O$, room temp., 15 h; (b) (i) Et_3N (1.5 equiv.), $ClCO_2Et$ (1.5 equiv.), THF, 0 °C, 30 min, (ii) NaN_3 (50 equiv.), 0 °C, 30 min; (d) (i) toluene, 100 °C, (ii) BnOH (1.1 equiv.), 100 °C, 15 h.

the borates into the cyclopropanes **16** failed, even when the most reliable coupling partner iodobenzene was used, and optimised protocols from our own group or alternative catalyst systems (e.g., from the Buchwald[21] or the Glorius[22] groups) were applied. It is noteworthy that in all cases in which an acidic proton on the nitrogen atom was involved (carbamates **15a**, **15c**) the NMR spectra of the crude products did not show any cyclopropane signals after the transformation, making ring-opening under basic conditions likely. With the phthalimide-substituted cyclopropane **15b** the product was also not obtained, but deboronation was observed to a minor extent when Deng conditions[18b] were applied.



Scheme 4. Potasium trifluoroborates **15** and attempted cross-coupling.

The side-reactions could obviously only be avoided under nonprotic conditions, a prerequisite that could not be met with trifluoroborates. Matteson et al. have recently reported a convenient alternative in which trifluoroborates were transformed into more reactive dichloroboranes.[23] We utilised this approach and converted the phthalimide **15b** with $SiCl_4$; the intermediate dichloride was then directly treated first with MeOH and then with propane-1,3-diol, leading to the corresponding 1,3,2-dioxaborinane **17** in 87% yield (Scheme 5). The ester **17** is a colourless solid that can be conveniently stored for a long time at 4 °C under dry nitrogen; it also crystallised from $CDCl_3$, allowing for an X-ray structure analysis.[24] First attempts to perform cross-coupling reactions with 10 mol-% catalyst were disappointing (Scheme 5, Entry 1). In order to evaluate whether the transformation took place at all, 1 equiv. of $Pd(PPh_3)_4$ was added. Although no product **16b** was observed at 100 °C after 1 h (Entry 2), minor amounts (20% yield, Entry 3) were isolated after 36 h. Obviously, the purification was hampered by the large amounts of ligand present, also accounting for the low yield. We tried to reduce the Pd^0 loading (Entries 4 and 5), but were not able to increase the yield beyond 40% [Entry 4, 0.5 equiv. $Pd(PPh_3)_4$]. In summary, although the desired aminocyclopropylboronates could be synthesised and used for Suzuki couplings, they proved to be impractical for large-scale syntheses of a library of enantiomerically pure aminocyclopropanes. An alternative route utilizing the C–B to C–N conversion was hence pursued.



Entry	$Pd(PPh_3)_4$	PhI	Time [h]	Yield [%]
1	0.1 equiv.	1.2 equiv.	36	traces
2	1.0 equiv.	1.2 equiv.	1	–
3	1.0 equiv.	1.2 equiv.	36	20
4	0.5 equiv.	0.9 equiv.	36	40
5	0.2 equiv.	0.9 equiv.	36	14

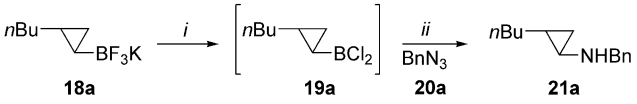
Scheme 5. Conditions: (a) (i) $SiCl_4$ (2.0 equiv.), THF, room temp., 1 h, (ii) MeOH (11.0 equiv.), 0 °C, 10 min, (iii) propane-1,3-diol (1.1 equiv.), 0 °C to room temp.

Cyclopropylamines by C–B to C–N Conversion

The fact that trifluoroborates could readily be converted into dichloroboranes stimulated the second approach, because it had been well established by Matteson et al. that these could be further transformed by treatment with azides in a one-pot procedure.[23a] In order to apply the method, all starting materials were first synthesised by standard procedures.[25–27]

For the optimisation study, the cyclopropyl trifluoroborate **18a** was converted into the dichloride **19a**, followed by treatment with benzyl azide[27] (**20a**, Scheme 6). The first experiment was run at room temperature in pure toluene, and we were pleased to obtain a 65% yield of the spectroscopically pure racemic amine **21a** directly (Entry 1). However, when acetonitrile (approximately 11%) was added to

the reaction mixture the solubility of trifluoroborate **18a** was increased, as was the yield (72%, Entry 2). An increase in the temperature to 60 °C improved the yield further and allowed for a shorter reaction time (Entry 3), but some impurities were observed. Consequently, 40 °C was taken as the temperature of choice for the second step, and for convenience we increased the amount of acetonitrile for all subsequent experiments to 20%. We next checked the yield as a function of reaction time (Entries 4–8) and obtained the highest yield when the reaction was quenched after 10–15 h (Entry 7); prolonged reaction times did not increase the yield further.



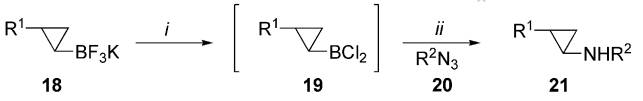
18a **19a** **20a** **21a**

Entry	Conditions	Yield
1	*i*: 2 equiv. $SiCl_4$, toluene, r.t., 20 min; *ii*: 1.4 equiv. BnN_3, r.t., 24 h	65%
2	*i*: 2 equiv. $SiCl_4$, toluene/CH_3CN (8:1), r.t., 20 min; *ii*: 1.4 equiv. BnN_3, r.t., 24 h	72%
3	*i*: 2 equiv. $SiCl_4$, toluene/CH_3CN (4:1), r.t., 20 min; *ii*: 1.4 equiv. BnN_3, 60 °C, 5 h	78%*
4	*i*: 2 equiv. $SiCl_4$, toluene/CH_3CN (4:1), r.t., 20 min; *ii*: 1.4 equiv. BnN_3, 40 °C, 1 h	60%
5	*i*: 2 equiv. $SiCl_4$, toluene/CH_3CN (4:1), r.t., 20 min; *ii*: 1.4 equiv. BnN_3, 40 °C, 3 h	65%
6	*i*: 2 equiv. $SiCl_4$, toluene/CH_3CN (4:1), r.t., 20 min; *ii*: 1.4 equiv. BnN_3, 40 °C, 6 h	74%
7	*i*: 2 equiv. $SiCl_4$, toluene/CH_3CN (4:1), r.t., 20 min; *ii*: 1.4 equiv. BnN_3, 40 °C, 15 h	81%
8	*i*: 2 equiv. $SiCl_4$, toluene/CH_3CN (4:1), r.t., 20 min; *ii*: 1.4 equiv. BnN_3, 40 °C, 24 h	76%

Scheme 6. Optimisation of the aminocyclopropane synthesis (* contained impurities).

The optimised reaction conditions [toluene/acetonitrile (4:1), 40 °C, 15 h] were applied in other amine syntheses (Scheme 7). After the alkyl-substituted cyclopropane **18a** (Entry 1, for comparison), the phenylcyclopropane **18b** was used. Independently of the azide used, high yields were obtained [Entry 2: **21b** (86%) from benzyl azide (**20a**); Entry 3: **21c** (80%) from *p*-methoxybenzyl azide (**20b**); Entry 4: **21d** (85%) from allyl azide (**20c**)]. In order to avoid possible evaporation of allyl azide (**20c**), the reaction was carried out at room temperature.

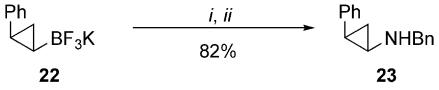
Although the benzyl-protected trifluoroborate **18c** could not be successfully converted into amine **21a** – Lewis acidic conditions at elevated temperatures were not tolerated – the benzoyl-protected derivative **18d** could be used conveniently, furnishing the benzylamine **21f** in 73% yield (Entry 6). However, the transformation was stopped after 5 h, because prolonged heating caused the formation of undesired side-products. The reaction of the *cis*-cyclopropane **22**[18b] also proceeded smoothly, affording amine **23** in 82% yield.



18 **19** **20** **21**

Entry	R^1	R^2	Yield
1	*n*Bu (**18a**)	Bn (**20a**)	81% (**21a**)
2	Ph (**18b**)	Bn (**20a**)	86% (**21b**)
3	Ph (**18b**)	PMB (**20b**)	80% (**21c**)
4	Ph (**18b**)	allyl (**20c**)	85%* (**21d**)
5	$BnOCH_2$ (**18c**)	Bn (**20a**)	– (**21e**)
6	$BzOCH_2$ (**18d**)	Bn (**20a**)	73%** (**21f**)

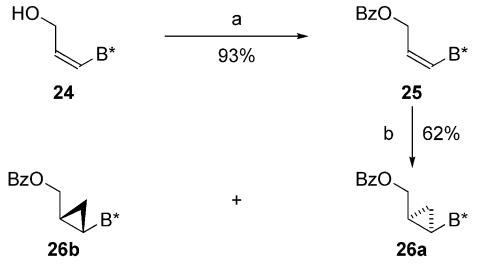
* The reaction mixture was stirred at r.t.
** The reaction mixture was stirred for 5 h.



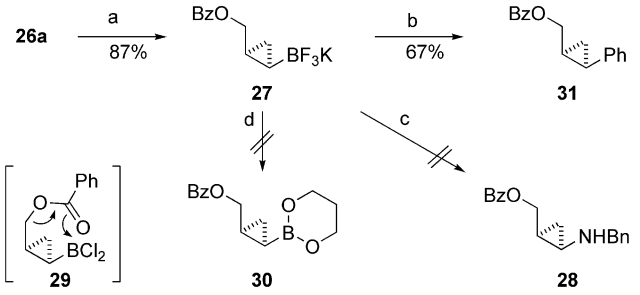
22 **23**

Scheme 7. Conditions: (i) $SiCl_4$ (2 equiv.), toluene/CH_3CN (4:1), room temp., (ii) **20a** (1.4 equiv.), 40 °C, 15 h.

In view of the results obtained with the *trans* series, we next investigated enantiomerically pure functionalised *cis*-substituted cyclopropanes. Protected (hydroxymethyl)cyclopropanes are ideal model compounds with the flexibility for the introduction of a number of functional groups. For obvious reasons, neither silyl or benzyl ethers nor acetals were chosen, but again the benzoate was selected, because none of the other groups would tolerate the Lewis acidic conditions (or the fluoride reagent). The target compound was not known prior to the present investigation; it was synthesised from the established[16c,16q] (*Z*)-allyl alcohol **24** through the introduction of the protecting group (Scheme 8, 93% yield). Cyclopropanation was – as expected – only possible with the $Pd(OAc)_2$-catalysed decomposition of diazomethane, furnishing the cyclopropanes **26a** and **26b** in 63% yield as a separable 1:1 mixture. It had already been shown that the diastereoselectivity in the *cis* series was relatively low,[17c] and consequently we did not attempt to optimise the diastereomeric ratio of the conversion, because both isomers were required anyway. However, the following investigation was disappointing: after successful conversion into the trifluoroborate **27** (Scheme 9, 87% yield), all attempts to perform the amination (desired product **28**) failed. We speculated that the high reactivity of the dichloroborane species **29**, with the proximity of the carbonyl group, was enhancing the intramolecular reaction leading to ring-opening and decomposition. In order to confirm the result, we also investigated the transformation via **29** into the 1,3,2-borinane **30**, which – as expected – failed. Omitting the electrophilic boron intermediate, we also performed a Suzuki coupling to afford cyclopropane **31**, which proceeded as expected (67% yield).

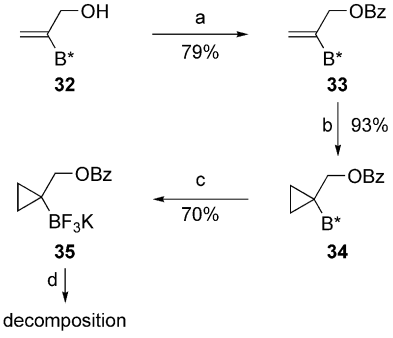


Scheme 8. Conditions: (a) BzCl (1.2 equiv.), DMAP (3 mol-%), Et_3N (1.0 equiv.), CH_2Cl_2, 15 h; (b) CH_2N_2 (12 equiv.), $Pd(OAc)_2$ (0.1 equiv.), Et_2O, 0 °C.



Scheme 9. Conditions: (a) KHF_2 (50 equiv.), MeOH, 80 °C; (b) PhBr (1.2 equiv.), Cs_2CO_3 (3 equiv.), $PdCl_2(dppf)\cdot CH_2Cl_2$ (7 mol-%), THF/H_2O (3:1), 60 °C, 15 h; (c) (i) $SiCl_4$ (2 equiv.), toluene/CH_3CN (4:1), room temp., (ii) BnN_3 (1.4 equiv.), 40 °C, 5 h; (d) (i) $SiCl_4$ (2.0 equiv.), THF, room temp., 1 h, (ii) MeOH (11.0 equiv.), 0 °C, 10 min, (iii) propane-1,3-diol (1.1 equiv.) , 0 °C to room temp.

The same argument of a proximity effect should also hold true for a related derivative that was synthesised from the known[19,16q] 2-substituted allyl alcohol **32** (Scheme 10): the three-step sequence – protection (ester **33** in 79% yield), cyclopropanation (cyclopropane **34** in 93% yield) and formation of trifluoroborate **35** (70% yield) – was uneventful. Again, the following steps failed to provide the desired amine, with only decomposition being observed.



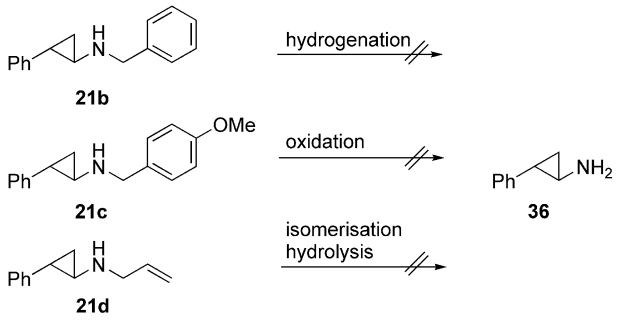
Scheme 10. Conditions: (a) BzCl (3.0 equiv.), Et_3N (2.0 equiv.), DMAP (0.1 equiv.), CH_2Cl_2, room temp., 15 h; (b) $Pd(OAc)_2$ (5 mol-%), CH_2N_2 (12 equiv.), Et_2O, 0 °C, 30 min; (c) KHF_2 (50 equiv.), MeOH, 80 °C, 2 d; (d) (i) $SiCl_4$ (2 equiv.), toluene/CH_3CN (4:1), room temp., (ii) BnN_3 (1.4 equiv.), room temp., 5 h.

In summary, we have devised a method for the synthesis of cyclopropylamines from cyclopropylboronic esters through a C–B to C–N conversion. The scope in view of possible protecting groups to use and thus the limitations, especially for the *cis*-substituted cyclopropanes, was demonstrated. In the final section two applications of the developed approach are discussed.

Applications

Tranylcypromine (**36**, Parnate®, Jatrosom®; see Figure 1) is a clinically useful agent for the treatment of mental depression and certain phobic anxieties in patients who do not respond to other therapies; they must be either closely supervised or hospitalised.[3b,28] The drug acts as a monoamine oxidase (MAO) inhibitor, and the mechanism involved in MAO inhibition has been studied in detail.[29] Although the drug is commercially available as racemic mixture, it has been shown that the (1*S*,2*R*) isomer is four times more potent than its enantiomer.[30] Tranylcypromine is commonly synthesised from the corresponding acid by a Curtius rearrangement,[13h] but for the synthesis of enantiomerically pure products, kinetic enzymatic resolutions have been used as key steps.[3c,3d,30b,31]

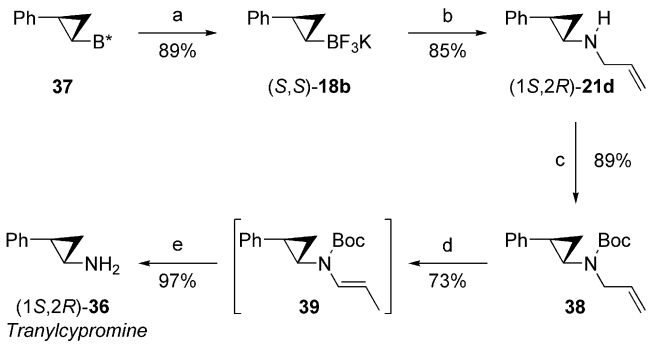
Before proceeding with attempts directed towards the enantiomerically pure drug, we examined the deprotection of the synthesised racemic amines **21b**–**d** (Scheme 11). Obviously, the task at hand was not unproblematic, because attempted hydrogenolysis of benzylamine **21b** (even at –20 °C) led to ring-opening, as did the oxidative cleavage of the PMB group in amine **21c** – probably through a mechanism similar to that of the MAO inhibition. A variety of conditions were tested for the isomerisation/hydrolysis sequence necessary to deprotect the allylamine **21d**, but the high temperatures needed for the isomerisation led to decomposition of the formed product **36**. Because Boc-protected tranylcypromine is stable up to high temperatures, this protection of the allylamine was assumed to be the method of choice for the following investigation.



Scheme 11. Attempts to deprotect amines **21b**–**d**.

Scheme 12 summarises the successful synthesis of enantiomerically pure tranylcypromine (**36**). From the starting enantio- and diastereoisomerically pure cyclopropylboronic ester **37**,[19a] the corresponding trifluoroborate (*S*,*S*)-**18b** was first obtained in 89% yield. As expected, the amine synthesis proceeded smoothly, yielding the allylamine

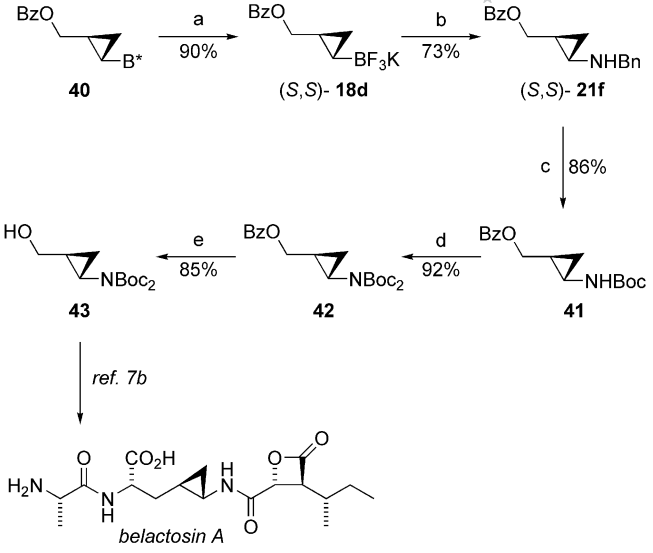
(1*S*,2*R*)-**21d** in 85% yield. The Boc group was readily introduced by a standard procedure with Boc_2O, furnishing carbamate **38** in 89% yield, and the isomerisation to the enamine **39** was conveniently achieved with an Ru catalyst[32] in deoxygenated xylene in 73% yield. The subsequent hydrolysis of enamine **39** with HCl in THF failed to give the desired product **36**. Nevertheless, when trifluoroacetic acid (TFA) in a dioxane/H_2O (2:1) mixture as solvent at 50 °C was used instead, the corresponding TFA salt of tranylcypromine was obtained in quantitative yield. Treatment of the salt with aqueous KOH and extraction with Et_2O liberated the enantiomerically pure tranylcypromine [(1*S*,2*R*)-**36**] (quant.).



Scheme 12. Conditions: (a) KHF_2 (50 equiv.), MeOH, 80 °C, 2 d; (b) (i) $SiCl_4$ (2 equiv.), toluene/CH_3CN (4:1), room temp., (ii) $AllylN_3$ (1.4 equiv.), room temp., 15 h; (c) Et_3N (1.3 equiv.), DMAP (0.3 equiv.), Boc_2O (3 equiv.), CH_3CN, room temp., 2 d; (d) $HRu(PPh_3)_3$·toluene (1–10 mol-%), xylene, 138 °C, 15 h; (e) TFA, dioxane/H_2O (2:1), 50 °C, 15 h.

A second application was devised for a known key intermediate of the belactosin A synthesis.[7b] Belactosin A is a *Streptomyces* metabolite that displays inhibitory activity towards cyclin–cyclin-dependent kinase complexes;[7a] it has been demonstrated to inhibit the cell cycle progression of human tumour cells at the G2/M phase. It has also been shown to be a ubiquitin-proteasome inhibitor.[7e,7f] The total synthesis has been accomplished by different groups,[7b–7d] but the cyclopropane-containing core amino acid in particular has been the object of several studies.[13a,33] The amination of trifluoroborates reported in this manuscript offers an alternative (Scheme 13).

The pure benzoate **40**[16d] was again readily converted into the enantiomerically pure (*S*,*S*)-**18d** (90% yield), followed by the established amination via the dichloroborane with benzyl azide (**20a**) [(*S*,*S*)-**21f**, 73% yield]. Removal of the benzyl group by hydrogenolysis in the presence of Boc_2O[34] led directly to carbamate **41**; however, the two-step sequence (Boc protection followed by hydrogenolysis) proved to be more reliable, giving the desired product **41** in 86% yield. Two consecutive protecting group manipulations (Boc protection; **42**: 92% yield; saponification; **43**: 85% yield) led to the desired enantiomerically pure building block that has been used previously in the total synthesis of belactosin A.[7b]



Scheme 13. Conditions: (a) KHF_2 (50 equiv.), MeOH, 80 °C, 2 d; (b) (i) $SiCl_4$ (2 equiv.), toluene/CH_3CN (4:1), room temp., (ii) BnN_3 (1.4 equiv.), **20**, room temp., 5 h; (c) (i) Boc_2O (1.5 equiv.), Et_3N (1.5 equiv.), MeOH, room temp., 20 h, (ii) Pd/C (10 mol-%), H_2, 3 d; (d) DMAP (0.3 equiv.), Boc_2O (3 equiv.), CH_3CN, room temp., 15 h; (e) NaOH (7 equiv.), MeOH, 30 min.

Conclusions

The versatility of highly stable enantio- and diastereomerically pure cyclopropylboronic esters was confirmed, and the scope was extended by (a) their conversion into the corresponding trifluoroborates and (b) exploitation of the boron moiety for the synthesis of amines. The high-yielding transformations could be successfully applied to the partial and total synthesis of the biologically active products belactosin A and tranylcypromine (**36**). The limitations with respect to *cis*- and 1,1-disubstituted cyclopropanes were shown, forming the foundation for future endeavours.

Experimental Section

General Remarks: All reagents were used as purchased from commercial suppliers without further purification. The reactions were carried out by standard Schlenk techniques under dry nitrogen. Glassware was oven-dried at 112 °C overnight. Solvents were dried and purified prior to use. 1,2-Dimethoxyethane (DME) and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone. Toluene, dichloromethane (CH_2Cl_2) and diethyl ether (Et_2O) were dried with the aid of a Solvent Purification System (MBraun, MB SPS-800). Petroleum ether refers to the fraction with a boiling range of 40–60 °C. Flash-column chromatography: Macherey–Nagel silica gel 0.040–0.063 mm (400–230 mesh). TLC: pre-coated sheets of silica gel 60 with a fluorescence indicator (Alugram® SIL G/UV_{245}, Macherey–Nagel), detection by UV extinction (245 nm) or with cerium molybdenum solution [phosphomolybdic acid (25 g), $Ce(SO_4)_2$·H_2O (10 g), concd. H_2SO_4 (60 mL), H_2O (940 mL)], with ninhydrin solution [ninhydrin (3.2 g), acetone (200 mL)] or with vanillin solution. Preparative MPLC: Labomatic

(MD80/100), with a packed column (39 × 400 mm or 23 × 250 mm), LiChroprep, Si60 (15–25 μm) and UV detector (254 nm). ^{1}H and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ unless otherwise stated with a Bruker ARX 300, ARX 500 or DRX 600, or a Varian Inova 400. Chemical shifts (δ) are given in ppm relative to internal standard TMS (^{1}H: δ = 0.00 ppm) or relative to the resonance of the solvent (e.g., ^{1}H: $CHCl_3$, δ = 7.25 ppm; ^{13}C: $CHCl_3$, δ = 77.0 ppm). In the case of ^{19}F and ^{11}B NMR spectra the external standard $BF_3{\cdot}OEt_2$ (δ = 0.0 ppm) was used. *J* values (coupling constants) are given in Hz; in spectra of higher order the δ and *J* values were not corrected. The multiplicities of the signals are given as the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), m_c (centred multiplet), br. (broad signal). The NMR signals were assigned by means of DEPT, H-H and C-H COSY spectroscopy. The diastereomeric ratios were determined by the integration of the corresponding signals in the ^{1}H or ^{13}C NMR spectra. Microanalyses were performed at the Institut für Organische Chemie, Stuttgart. Melting points (Büchi Melting Point SMP-20, Büchi Melting Point B-540 and Stuart Melting Point SMP3) are not corrected. Specific rotations were measured at 20 °C unless otherwise stated.

Representative Procedure for the Curtius Rearrangement

Benzyl Carbamate 10a: Acyl azide **8** (0.62 g, 1.08 mmol) was dissolved in dry toluene (5.00 mL) under dry nitrogen, and benzyl alcohol (1.11 mL, 1.10 mmol) was added. The mixture was stirred under reflux at 110 °C for 4 h and was then allowed to cool to room temp., and toluene was removed under reduced pressure. The crude product was purified by column chromatography [silica gel (60 g), PE/EtOAc (85:15)] to yield amine **10a** (0.59 g, 0.90 mmol, 84%) as a colourless solid, m.p. 88–89 °C. $[\alpha]_D^{20}$ = –26.3 (*c* = 0.30, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = –0.36 (ddd, *J* = 10.5, *J* = 7.3, *J* = 4.1 Hz, 1 H, 1′-H), 0.58 (ddd, *J* = 10.5, *J* = 4.1, *J* = 4.1 Hz, 1 H, 3′-H_b), 0.63 (ddd, *J* = 10.7, *J* = 7.3, *J* = 4.1 Hz, 1 H, 3′-H_a), 2.16 (ddd, *J* = 10.7, *J* = 4.1, *J* = 4.1 Hz, 1 H, 2′′-H), 2.99 (s, 6 H, OCH_3), 4.67 (br., 1 H, NH), 5.05 (s, 2 H, 1′′-H), 5.27 (s, 2 H, 4-H, 5-H), 7.33–7.28 (m, 25 H, arom. CH) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 2.0 (C-1′), 13.1 (C-3′), 28.9 (C-2′), 51.7 (OCH_3), 66.6 (C-1′′), 77.7 (C-4 and C-5), 83.2 (CPh_2OCH_3), 127.3, 127.4, 127.6, 127.8, 128.1, 128.4, 128.5, 129.7 (arom. CH), 136.5, 141.1 (arom. C_{ipso}), 156.4 (CO) ppm. IR (film): $\tilde{\nu}$ = 3316, 3061, 3031, 1709, 1417, 1185, 1075, 906, 729, 697 cm^{-1}. MS (FAB, NBA + NaI): *m*/*z* (%) = 676.3 (100) $[M + Na]^+$, 197.1 (76) $[Ph_2CO{-}CH_3]^+$. $C_{41}H_{40}BNO_6$ (653.57): calcd. C 75.35, H 6.17, N 2.14; found C 75.19, H 6.17, N 2.16.

Representative Procedure for the Trifluoroborate Formation

Trifluoroborate (*S*,*S*)-15a: Cyclopropylboronic ester **10a** (0.59 g, 0.90 mmol) was dissolved in a minimum amount of CH_2Cl_2 in a Teflon flask. KHF_2 (3.53 g, 45.2 mmol) and MeOH (100 mL) were added, and the mixture was stirred at 80 °C for 4 d. After full conversion, the solvent was removed under reduced pressure. The cleaved diol was removed from the cake by filtration with Et_2O. The trifluoroborate was then dissolved in abundant CH_3CN, and the remaining KHF_2 was filtered through a Büchner funnel with CH_3CN. After concentration of the solvent under reduced pressure, the trifluoroborate (*S*,*S*)-**15a** (0.21 g, 0.71 mmol, 78%) was obtained as a colourless solid, m.p. 185–188 °C. $[\alpha]_D^{20}$ = +32.0 (*c* = 0.50, MeOH). ^{1}H NMR ([D_6]DMSO, 60 °C, 400 MHz): δ = –0.50 (ddd, *J* = 10.8, *J* = 7.5, *J* = 4.5 Hz, 1 H, 1-H), 0.03 (ddd, *J* = 7.5, *J* = 6.1, *J* = 3.0 Hz, 1 H, 3-H_a), 0.17 (ddd, *J* = 10.8, *J* = 3.0, *J* = 3.0 Hz, 1 H, 3-H_b), 2.21 (ddd, *J* = 6.1, *J* = 4.5, *J* = 3.0 Hz, 1 H, 2-H), 4.99 (s, 2 H, 1′-H), 6.70 (br., 1 H, NH), 7.28–7.37 (m, 5 H, arom. CH) ppm. ^{13}C NMR ([D_6]DMSO, 100 MHz): δ = 10.3 (C-3), 27.5 (C-2), 65.1 (C-1′), 53.3 (C-1′′), 127.9, 128.7 (arom. CH), 138.0 (arom. C_{ipso}), 157.1 (CO) ppm (C-1 not detectable). ^{19}F NMR ([D_6]DMSO, 376 MHz): δ = –136.6 (s, 1 F, BF_2OMeK; impurity), –140.2 (s, 14 F, BF_3K) ppm. IR (film): $\tilde{\nu}$ = 3639, 3579, 3361, 3306, 3028, 2943, 2898, 1714, 1672, 1534, 1514, 1454, 1389, 1299, 1266, 1217, 1177, 1096, 1048, 990, 940, 912, 869, 779, 734, 696 cm^{-1}. MS (ESI, positive ion): *m*/*z* (%) = 270.7 $[M + OMe - KF]^+$ (100), 239.4 $[M - KF]^+$ (63).

Representative Procedure for the C–B to C–N Conversion

Amine 21a (HCl Salt): Cyclopropyl trifluoroborate **18a** (45.0 mg, 0.22 mmol) was suspended in toluene (2.20 mL)/CH_3CN (0.55 mL) under dry nitrogen. $SiCl_4$ (0.44 mL of a 1 M solution in CH_2Cl_2, 0.44 mmol) was added at room temp., and the mixture was stirred for 20 min. Benzyl azide (**20a**, 0.04 g, 0.31 mmol) was added, and the reaction mixture was stirred at 40 °C for 15 h. The reaction was quenched with water (2.20 mL), and the layers were separated. The organic layer was extracted with HCl (1 M, 5 × 2.20 mL). The combined aqueous layers were strongly basified with aq. KOH (40%). The amine was extracted with diethyl ether (4 × 10 mL). The combined ether layers were dried with Na_2CO_3, and the solvent was removed under reduced pressure. The amine **21a** (36.0 mg, 0.77 mmol, 81%) was obtained as yellow oil. For convenience during characterisation, the hydrochloride was formed upon titration with HCl as a colourless solid, m.p. 126–128 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 0.52 (m_c, 1 H, 3-H_a), 0.84 (t, *J* = 7.0 Hz, 3 H, 4′-H), 1.02 (m_c, 1 H, 1′-H_a), 1.23 (m_c, 1 H, 3-H_b), 1.23–1.29 (m, 5 H, 1′-H_b, 2′-H, 3′-H), 1.48 (m_c, 1 H, 2-H), 2.03 (m_c, 1 H, 1-H), 4.04 (s, 2 H, CH_2Ph) 7.34–7.42 (m, 3 H, arom. CH), 7.58–7.63 (m, 2 H, arom. CH), 9.91 (br., 2 H, NH_2) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 0.4 (C-3), 13.9 (C-4′), 17.6 (C-2), 22.3 (C-3′), 30.6 (C-2′), 31.2 (C-1′), 34.4 (C-1), 51.3 (CH_2Ph), 128.9, 129.3, 130.6 (arom. CH), 130.2 (arom. C_{ipso}) ppm. IR (film): $\tilde{\nu}$ = 2957, 2923, 2857, 2700, 2522430, 1584, 1493, 1467, 1455, 1443, 1410, 1392, 1377, 1246, 1215, 1153, 1085, 1055, 1026, 993, 917, 874, 749, 729, 694 cm^{-1}. MS (ESI, positive ion): *m*/*z* (%) = 204.3 $[M - Cl]^+$ (100). $C_{14}H_{22}ClN$ (239.78): calcd. C 70.13, H 9.32, N 5.84; found C 69.88, H 9.10, N 5.81.

Synthesis of Tranylcypromine (36)

Trifluoroborate 18b: Cyclopropylboronic ester **37**[19a] (0.56 g, 0.96 mmol) was treated with KHF_2 (3.77 g, 48.2 mmol) in MeOH (200 mL) for 2 d according to the procedure described for compound (*S*,*S*)-**15a**. The cyclopropyl trifluoroborate (*S*,*S*)-**18b** (0.19 g, 0.86 mmol, 89%) was obtained as a colourless solid, m.p. 222–234 °C (decomposition). $[\alpha]_D^{20}$ = +35.0 (*c* = 1.25, MeOH). ^{1}H NMR ([D_4]MeOH, 600 MHz): δ = –0.05 (ddd, *J* = 7.4, *J* = 3.6, *J* = 5.3 Hz, 1 H, 1-H), 0.53 (ddd, *J* = 10.0, *J* = 2.6, *J* = 3.6 Hz, 1 H, 3-H_a), 0.80 (ddd, *J* = 7.4, *J* = 2.6, *J* = 7.4 Hz, 1 H, 3-H_b), 1.66 (ddd, *J* = 10.0, *J* = 5.3, *J* = 7.4 Hz, 1 H, 2-H), 6.99–7.17 (m, 5 H, arom. CH) ppm. ^{13}C NMR ([D_4]MeOH, 151MHz): δ = 14.7 (C-3), 19.94 (C-2), 125.0, 126.2, 128.8 (arom. CH), 148.9 (arom. C_{ipso}) ppm (C-1 not detectable). ^{19}F NMR ([D_4]MeOH, 564 MHz): δ = –144.6 (br. s, BF_3K) ppm. ^{10}B NMR ([D_4]MeOH, 64 MHz): δ = 4.0 (br., BF_3K) ppm. IR (film): $\tilde{\nu}$ = 3061, 3002, 3018, 2987, 2960, 1602, 1494, 1457, 1391, 1315, 1276, 1184, 1162, 1123, 1107, 1072, 1057, 1102, 987, 952, 925, 902, 884, 861, 757, 696 cm^{-1}. MS (ESI, negative ion): *m*/*z* (%) = 184.3 $[M - K]^-$ (57). Spectroscopic data are in full agreement with those previously reported.[18b]

(1*S*,2*R*)-Amine 21d (HCl Salt): Phenylcyclopropyl trifluoroborate (*S*,*S*)-**18b** (0.17 g, 0.76 mmol) was treated with $SiCl_4$ (0.52 mL of a 1 M solution in CH_2Cl_2, 0.52 mmol) according to the procedure

described for compound **21a**. Allyl azide (**20c**, 0.25 g, 1.06 mmol) was then added, and the mixture was stirred at room temp. for 14 h. The amine **21d** (0.11 g, 0.65 mmol, 85%) was obtained as yellow oil. The hydrochloride (0.09 g, 0.44 mmol, 58%) was obtained as a brown solid, m.p. 107–109 °C. $[\alpha]_D^{20}$ = +64.6 (*c* = 0.35, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.26 (ddd, *J* = 7.7, *J* = 6.6, *J* = 6.5 Hz, 1 H, 3-H_b), 1.86 (ddd, *J* = 10.2, *J* = 6.6, *J* = 4.4 Hz, 1 H, 3-H_a), 2.73 (ddd, *J* = 7.7, *J* = 4.4, *J* = 3.6 Hz, 1 H, 1-H), 2.83 (ddd, *J* = 10.2, *J* = 6.5, *J* = 3.6 Hz, 1 H, 2-H), 3.72 (m_c, 2 H, 1′-H), 5.44 (dd, *J* = 10.2, *J* = 1.0 Hz, 1 H, 3′-H_a), 5.50 (dd, *J* = 17.1, *J* = 1.0 Hz, 1 H, 3′-H_b), 6.15 (ddt, *J* = 17.1, *J* = 10.2, *J* = 6.9 Hz, 1 H, 2′-H), 7.09–7.31 (m, 5 H, arom. CH), 10.14 (br., 2 H, NH_2) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 12.9 (C-3), 21.4 (C-2), 37.1 (C-1), 50.5 (*C*H_2Ph), 124.3 (C-3′), 126.6, 126.9, 128.5, 128.7 (arom. CH), 127.6 (C-2′), 137.9 (arom. C_{ipso}) ppm. IR (film): $\tilde{\nu}$ = 3090, 3042, 2951, 2895, 2849, 2780, 2739, 2717, 2687, 2605, 2513, 2437, 2417, 1604, 1585, 1497, 1464, 1454, 1440, 1423, 1183, 1047, 989, 941, 909, 838, 762, 739, 695 cm^{-1}. MS (ESI, positive ion): *m*/*z* (%) = 174.2 $[M - Cl]^+$ (100). $C_{12}H_{16}ClN$ (209.72): calcd. C 68.73, H 7.69, N 6.68; found C 68.69, H 7.70, N 6.67.

(1*S*,2*R*)-Carbamate 38: Allylamine **21d** (0.23 g, 1.32 mmol) was dissolved in dry CH_3CN (15.0 mL) under dry nitrogen. Boc_2O (0.86 g, 3.96 mmol) and DMAP (48 mg, 0.39 mmol) were added, and the mixture was stirred at room temp. overnight. After complete conversion (as judged by TLC), the solvents were removed under reduced pressure, and the crude product was purified by column chromatography [silica gel (20 g), PE/EtOAc (90:10)] to yield carbamate **38** (0.32 g, 1.17 mmol, 89%) as a colourless oil. $[\alpha]_D^{20}$ = +49.0 (*c* = 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.18 (ddd, *J* = 7.4, *J* = 6.3, *J* = 5.9 Hz, 1 H, 3-H_a), 1.29 (ddd, *J* = 9.7, *J* = 5.9, *J* = 4.5 Hz, 1 H, 3-H_b), 1.43 (s, 9 H, C*H*$_3$), 2.14 (ddd, *J* = 9.7, *J* = 6.3, *J* = 3.3 Hz, 1 H, 2-H), 2.74 (ddd, *J* = 7.4, *J* = 4.5, *J* = 3.3 Hz, 1 H, 1-H), 3.84 (dddd, *J* = 15.9, *J* = 5.6, *J* = 1.5, *J* = 1.5 Hz, 1 H, 1′-H_a), 3.95 (m_c, 1 H, 1′-H_b), 5.11 (ddd, *J* = 10.2, *J* = 3.0, *J* = 1.5 Hz, 1 H, 3′-H_a), 5.14 (ddd, *J* = 17.1, *J* = 3.0, *J* = 1.5 Hz, 1 H, 3′-H_b), 5.84 (ddd, *J* = 17.1, *J* = 10.2, *J* = 5.6 Hz, 1 H, 2′-H), 7.09–7.27 (m, 5 H, arom. CH) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 17.4 (C-3), 26.2 (C-2), 28.5 (CH_3), 38.9 (C-1), 50.3 (C-1′), 79.8 [*C*$(CH_3)_3$], 115.9 (C-3′), 125.9, 126.2, 128.2 (arom. CH), 134.4 (C-2′), 141.0 (arom. C_{ipso}), 156.4 (CO) ppm. IR (film): $\tilde{\nu}$ = 2977, 2930, 1695, 1644, 1605, 1500, 1477, 1438, 1386, 1365, 1279, 1243, 1165, 1146, 1071, 1032, 992, 916, 861, 812, 774, 746, 696 cm^{-1}. MS (ESI, positive ion): *m*/*z* (%) = 312.0 (100) $[M + K]^+$. $C_{17}H_{23}NO_2$ (273.37): calcd. C 74.69, H 8.48, N 5.12; found C 74.49, H 8.45, N 5.05.

(1*S*,2*R*)-Enamine 39: Allylamine **38** (26.0 mg, 0.10 mmol) was dissolved in xylene (0.30 mL) under dry argon. After the solution had been deoxygenated by the freeze technique, $HRuCl(PPh_3)_3$·toluene (1–10 mol-%) was added, and the reaction mixture was stirred at 138 °C for 15 h. The crude product was directly subjected to column chromatography [silica gel (5 g), PE/EtOAc (98:2)], yielding the enamine **39** (19.0 mg, 70.0 μmol, 73%) as a colourless oil. $[\alpha]_D^{20}$ = +18.0 (*c* = 0.90, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.36 (ddd, *J* = 9.9, *J* = 5.9, *J* = 4.5 Hz, 1 H, 3-H_b), 1.39 (ddd, *J* = 7.5, *J* = 6.7, *J* = 5.9 Hz, 1 H, 3-H_a), 1.47 (s, 9 H, C*H*$_3$), 1.67 (dd, *J* = 6.6, *J* = 1.6 Hz, 1 H, 3′-H), 2.08 (ddd, *J* = 9.9, *J* = 6.7, *J* = 3.4 Hz, 1 H, 2-H), 2.58 (ddd, *J* = 7.5, *J* = 4.5, *J* = 3.4 Hz, 1 H, 1-H), 5.03 (dd, *J* = 20.6, *J* = 6.6 Hz, 1 H, 2′-H), 6.72 (br. d, 1 H, 1′-H), 7.11–7.30 (m, 5 H, arom. CH) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 15.5 (C-3′), 19.4 (C-3), 26.9 (C-2), 28.4 (CH_3), 35.9 (C-1), 80.8 [*C*$(CH_3)_3$], 105.7 (C-2′), 125.9, 126.0, 128.3 (arom. CH), 128.4 (C-1′), 140.9 (arom. C_{ipso}), 153.8 (CO) ppm. IR (film): $\tilde{\nu}$ = 2977, 2930, 1703, 1665, 1605, 1501, 1476, 1455, 1387, 1363, 1308, 1290, 1247, 1168, 1144, 1116, 1092, 1070, 1032, 1012, 999, 946, 915, 860, 813, 789, 768, 748, 696 cm^{-1}. MS (ESI, positive ion): *m*/*z* (%) = 296.2 (100) $[M + Na]^+$. HRMS (ESI, positive ion): calcd. for $C_{17}H_{23}NNaO_2$ 296.1621; found 296.1622.

(1*S*,2*R*)-2-Phenylcyclopropylamine [Tranylcypromine (36), HCl Salt]: Enamine **39** (17.0 mg, 60.0 μmol) was dissolved in dioxane (0.31 mL) and H_2O (0.15 mL) in a round-bottomed flask. After addition of TFA (0.15 mL), the reaction mixture was stirred at 50 °C for 15 h. After removal of the solvents under reduced pressure, the TFA amine salt (18 mg, 70 μmol, quant.) was obtained as a light yellow oil. The salt was dissolved in Et_2O (1 mL) and strongly basified with aqueous KOH (40%, 0.5 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (4 × 1 mL). The combined organic layers were dried with $MgSO_4$, and the solvents were removed under reduced pressure (not below 100 mbar!) to furnish tranylcypromine (**36**, 8.00 mg, 60.0 μmol, quant.) as a light yellow oil. The amine was precipitated (as described above for other amines) with concd. HCl vapours to yield the hydrochloride salt as a solid. $[\alpha]_D^{20}$ = +138 (*c* = 0.40, $CHCl_3$) [ref.[3d] *ent*-**36**: $[\alpha]_D^{20}$ = –135 (*c* = 0.81, $CHCl_3$)]. ^{1}H NMR (CD_3OD, 600 MHz): δ = 1.00 (ddd, *J* = 9.4, *J* = 5.3, *J* = 4.4 Hz, 1 H, 3-H_a), 1.04 (ddd, *J* = 7.4, *J* = 5.8, *J* = 5.3 Hz, 1 H, 3-H_b), 1.90 (ddd, *J* = 9.4, *J* = 5.8, *J* = 3.1 Hz, 1 H, 2-H), 2.49 (ddd, *J* = 7.4, *J* = 4.4, *J* = 3.1 Hz, 1 H, 1-H), 4.64 (br., 2 H, NH_2), 7.04–7.25 (m, 5 H, arom. CH) ppm. ^{13}C NMR (CD_3OD, 151 MHz): δ = 18.0 (C-3), 26.3 (C-2), 35.7 (C-1), 126.5, 126.7, 129.3 (arom. CH), 143.5 (arom. C_{ipso}) ppm. IR (film): $\tilde{\nu}$ = 2848, 2744, 2625, 2594, 1605, 1580, 1497, 1467, 1442, 1163, 1081, 1063, 1048, 1024, 937, 901, 800, 743, 698 cm^{-1}. MS (ESI, positive ion): *m*/*z* (%) = 133.9 (100) $[M + H]^+$. Spectroscopic data are in full agreement with those previously reported.[3d]

Synthesis of Belactosin A Intermediate 43

Trifluoroborate 18d: Cyclopropylboronic ester **40**[16d] (1.28 g, 2.00 mmol) was treated with KHF_2 (7.81 g, 100 mmol) in MeOH (300 mL) for 3 d according to the procedure described for compound (*S*,*S*)-**15a**. The trifluoroborate **18d** (1.01 g, 3.59 mmol, 90%) was obtained as a colourless solid, m.p. 195–199 °C. $[\alpha]_D^{20}$ = +23.7 [*c* = 0.50, MeOH/acetone (15:1)]. ^{1}H NMR ([D_6]acetone, 600 MHz): δ = –0.52 (ddd, *J* = 9.9, *J* = 6.8, *J* = 3.4 Hz, 1 H, 1-H), 0.11 (ddd, *J* = 9.9, *J* = 3.6, *J* = 3.0 Hz, 1 H, 3-H_b), 0.35 (dddd, *J* = 6.8, *J* = 6.8, *J* = 3.0, *J* = 1.0 Hz,1 H, 3-H_a), 1.00 (ddddd, *J* = 8.6, *J* = 6.8, *J* = 5.9, *J* = 3.6, *J* = 3.4 Hz, 1 H, 2-H), 3.85 (dd, *J* = 11.1, *J* = 8.6 Hz, 1 H, 1′-H_a), 4.34 (ddd, *J* = 11.1, *J* = 5.9, *J* = 1.0 Hz 1 H, 1′-H_b), 7.48–7.51 (m, 2 H, arom. CH), 7.60–7.62 (m, 1 H, arom. CH), 8.03–8.05 (m, 2 H, arom. CH) ppm. ^{13}C NMR ([D_6]acetone, 151 MHz): δ = 7.8 (C-3), 13.9 (C-2), 73.0 (C-1′), 129.3, 130.2, 133.5 (arom. CH), 132.1 (arom. C_{ipso}), 168.1 (CO) ppm (C-1 not detectable). ^{19}F NMR ([D_6]acetone, 564 MHz): δ = –143.5 (br. s, BF_3K) ppm. ^{10}B NMR ([D_6]acetone, 64 MHz): δ = 4.1 (br., BF_3K) ppm. IR (film): $\tilde{\nu}$ = 3062, 2993, 2942, 1706, 1600, 1553, 1454, 1400, 1315, 1277, 1096, 1067, 1023, 954, 925, 882, 869, 836, 814, 707, 686 cm^{-1}. MS (ESI, positive ion): *m*/*z* (%) = 243.6 (100) $[M - K + H]^+$.

(1*S*,2*S*)-Amine 21f (HCl Salt): Trifluoroborate (*S*,*S*)-**18d** (0.10 g, 0.35 mmol) was treated with $SiCl_4$ (0.71 mL of a 1 M solution in CH_2Cl_2, 0.71 mmol) for 5 min according to the procedure described for compound **21a**. Benzyl azide (**20a**, 0.07 g, 0.49 mmol) was then added, and the mixture was stirred at 40 °C for 5 h. The amine **21f** (0.07 mg, 0.26 mmol, 73%) was obtained as a yellow oil. The hydrochloride (0.08 g, 0.26 mmol, 73%) was obtained as a colourless solid, m.p. 135–138 °C (decomposition). $[\alpha]_D^{20}$ = –9.50 (*c* = 0.25, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.86 (ddd, *J* =

7.5, J = 6.6, J = 6.4 Hz, 1 H, 3-H_b), 1.49 (ddd, J = 10.4, J = 6.6, J = 4.2 Hz, 1 H, 3-H_a), 2.05 (ddddd, J = 10.4, J = 7.2, J = 6.4, J = 6.3, J = 3.8 Hz, 1 H, 1-H), 2.41 (ddd, J = 7.5, J = 4.2, J = 3.8 Hz, 1 H, 2-H), 4.00 (dd, J = 11.8, J = 7.2 Hz, 1 H, 1′-H_a), 4.07 (s, 2 H, CH_2Ph), 4.16 (dd, J = 11.8, J = 6.3 Hz, 1 H, 1′-H_b), 7.33–7.59 (m, 8 H, arom. CH), 8.00–8.03 (m, 2 H, arom.), 10.19 (br., 2 H, NH_2) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 8.9 (C-3), 16.2 (C-1), 33.3 (C-2), 51.6 (*C*H_2Ph), 64.5 (C-1′), 128.4, 129.1, 129.7, 130.6, 133.2 (arom. CH), 129.7, 129.9 (arom. C_{ipso}), 166.3 (CO) ppm. IR (film): $\tilde{\nu}$ = 2901, 2708, 2595, 2445, 1714, 1600, 1584, 1492, 1451, 1408, 1316, 1290, 1270, 1215, 1176, 1115, 1097, 1085, 1069, 1026, 1014, 999, 960, 882, 752, 696 cm^{-1}. MS (ESI, positive ion): m/z (%) = 282.2 (100) [M – Cl]$^+$. $C_{18}H_{20}ClNO_2$ (317.8): calcd. C 68.03, H 6.34, N 4.41; found C 67.86, H 6.36, N 4.25.

(1*S*,2*S*)-Benzoate 41: Amine (*S*,*S*)-**21f** (0.10 g, 0.36 mmol) was dissolved in MeOH (1.85 mL). Boc_2O (0.12 g, 0.53 mmol) and Et_3N (0.07 mL, 0.50 mmol) were added, and the mixture was stirred at room temp. overnight. After the conversion was complete (as judged by TLC), the solvents were removed under reduced pressure, and the crude product was purified by column chromatography [silica gel (10 g), PE/EtOAc (95:5)]. The product was dissolved in MeOH (4.00 mL) under dry nitrogen, and Pd/C (10%) (35 mg, 0.33 mmol) was added. The flask was then evacuated and flushed with hydrogen (repeated five times). The reaction mixture was stirred under H_2 for 3 d. After full conversion, the mixture was filtered through a pad of Celite® and silica gel that was thoroughly rinsed with CH_2Cl_2. The solvents were removed under reduced pressure, and the carbamate **41** (95.0 mg, 0.33 mmol, 86% over two steps) was obtained as a colourless solid, m.p. 94–96 °C (ref.[13g] m.p. 94–97 °C). $[\alpha]_D^{20}$ = +23.1 (c = 0.62, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 0.84–0.88 (m, 2 H, 3-H), 1.45 (s, 9 H, CH_3), 1.45 (m_c, 1 H, 1-H), 2.55–2.63 (m_c, 1 H, 2-H), 4.12–4.23 (m, 1 H, 1′-H_a), 4.30 (dd, J = 11.7, J = 6.9 Hz, 1 H, 1′-H_b), 4.42 (br., 1 H, NH), 7.42–7.59 (m, 4 H, arom. CH), 8.05–8.08 (m, 1 H, arom. CH) ppm. ^{13}C NMR ($CDCl_3$, 150 MHz): δ = 12.4 (C-3), 19.3 (C-1), 28.3 (C-2, *C*H_3), 66.5 (C-1′), 79.7 [*C*(CH_3)$_3$], 128.4, 129.6 (arom. CH), 130.3 (arom. C_{ipso}), 132.9 (arom. CH), 156.3 (NHCO), 166.6 (CO) ppm. IR (film): $\tilde{\nu}$ = 3365, 2983, 1713, 1683, 1601, 1586, 1508, 1469, 1452, 1392, 1366, 1316, 1283, 1268, 1247, 1168, 1158, 1116, 1069, 1027, 974, 946, 831, 796, 781, 708, 686, 672 cm^{-1}. Spectroscopic data are in full agreement with those reported previously.[13g]

(1*S*,2*S*)-Bis(carbamate) 42: Carbamate **41** (0.12 g, 0.40 mmol) was dissolved in dry CH_3CN (4.00 mL) under dry nitrogen. Boc_2O (0.26 g, 1.21 mmol) and DMAP (15.0 mg, 0.12 mmol) were added, and the mixture was stirred at room temp overnight. The solvents were removed under reduced pressure, and the crude product was purified by column chromatography [silica gel (20 g), PE/EtOAc (95:5)] to provide the carbamate **42** (0.14 g, 0.37 mmol, 92%) as a colourless solid, m.p. 98–99 °C. $[\alpha]_D^{20}$ = +35.5 (c = 0.55, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 0.96 (ddd, J = 9.4, J = 6.2, J = 4.0 Hz, 1 H, 3-H_a), 1.09 (ddd, J = 7.2, J = 6.8, J = 6.2 Hz, 1 H, 3-H_b), 1.51 (s, 18 H, CH_3), 1.51 (ddddd, J = 9.4, J = 8.0, J = 6.8, J = 5.4, J = 3.4 Hz, 1 H, 1-H), 2.63 (ddd, J = 7.2, J = 4.0, J = 3.4 Hz, 1 H, 2-H), 4.06 (dd, J = 11.5, J = 8.0 Hz, 1 H, 1′-H_a), 4.59 (dd, J = 11.5, J = 5.4 Hz, 1 H, 1′-H_b), 7.43–7.46 (m, 2 H, arom. CH), 7.55–7.57 (m, 1 H, arom. CH), 8.06–8.07 (m, 2 H, arom. CH) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 14.8 (C-3), 21.7 (C-1), 28.1 (*C*H_3), 32.7 (C-2), 65.9 (C-1′), 82.5 [*C*(CH_3)$_3$] 128.3, 129.7 (arom. CH), 130.3 (arom. C_{ipso}), 132.9 (arom. CH), 152.9 (CO), 166.6 (CO) ppm. IR (film): $\tilde{\nu}$ = 2984, 1766, 1711, 1599, 1578, 1449, 1368, 1332, 1296, 1269, 1253, 1156, 1090, 1068, 1041, 1025, 969, 951, 939, 921, 884, 852, 785, 714, 680, 672 cm^{-1}. MS (ESI, positive ion): m/z (%) = 414.2 (100) [M + Na]$^+$, 314.1 (79) [M + Na – $C_5H_9O_2$]$^+$. $C_{21}H_{29}NO_6$ (391.46): calcd. C 64.43, H 7.47, N 3.58; found C 64.20, H 7.45, N 3.43.

(1*S*,2*S*)-Alcohol 43: Carbamate **42** (0.10 g, 0.26 mmol) was dissolved in MeOH (10.0 mL) in a round-bottomed flask. NaOH (70.0 mg, 1.76 mmol) was added, and the mixture was stirred at room temp. for 30 min. CH_2Cl_2 was added, and the reaction mixture was quenched with satd. aq. NH_4Cl (3 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with satd. aq. $NaHCO_3$ (5 mL). The aqueous phase was extracted with CH_2Cl_2 (5 mL). The combined organic phases were dried with $MgSO_4$, and the solvents were removed under reduced pressure. The crude product was purified by column chromatography [silica gel (10 g), PE/EtOAc (81:19)], yielding the alcohol **43** as a colourless oil (62.0 mg, 0.22 mmol, 85%). $[\alpha]_D^{22}$ = +3.9 (c = 3.3, $CHCl_3$) [ref.[33b] *ent*-**43**: $[\alpha]_D^{22}$ = –3 (c = 2, $CHCl_3$)]. ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 0.94 (m_c, 2 H, 3-H), 1.31 (dddd, J = 12.8, J = 9.7, J = 4.8, J = 3.3 Hz, 1 H, 1-H), 1.51 (s, 18 H, CH_3), 2.46 (ddd, J = 6.8, J = 4.7, J = 3.3 Hz, 1 H, 2-H), 3.03 (br., 1 H, OH), 3.10 (dd, J = 10.9, J = 9.7 Hz, 1 H, 1′-H_a), 3.89 (dd, J = 10.9, J = 4.8 Hz, 1 H, 1′-H_b) ppm. ^{13}C NMR ($CDCl_3$, 151 MHz): δ = 13.7 (C-3), 24.9 (C-1), 28.0 (CH_3), 33.7 (C-2), 65.0 (C-1′), 82.9 [*C*(CH_3)$_3$], 153.5 (CO) ppm. IR (film): $\tilde{\nu}$ = 3506, 2980, 2937, 1738, 1706, 1687, 1478, 1457, 1429, 1365, 1326, 1274, 1248, 1231, 1158, 1118, 1093, 1047, 1021, 999, 940, 842, 788, 767, 756, 742 cm^{-1}. MS (ESI, positive ion): m/z (%) = 309.9 (100) [M + Na]$^+$. Spectroscopic data are in full agreement with those reported previously.[33b]

Supporting Information (see footnote on the first page of this article) Full experimental details for all compounds (**6–18**, **20–27**, **31**, **33–36**, **38**, **39**, **41–43**).

Acknowledgments

We gratefully acknowledge the Deutsche Forschungsgemeinschaft and the Otto-Röhm-Gedächtnisstiftung for the generous support of our projects. Donations from BASF AG, Chemetall GmbH and Wacker AG are greatly appreciated. Furthermore, we thank the analytical departments at the University of Stuttgart and the FZ Jülich as well as Vera Ophoven and Truc Pham for their support. We are especially grateful for the X-ray crystallographic analyses continuously provided by Dr. Wolfgang Frey.

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Received: August 3, 2009
Published Online: October 14, 2009

