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Tetrahedron 60 (2004) 9715–9723

Synthesis of both *syn* and *anti* diastereoisomers of Boc-dolaproine from (*S*)-proline through DKR using ruthenium-catalyzed hydrogenation: a dramatic role of *N*-protecting groups

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Received 18 June 2004; revised 2 July 2004; accepted 6 July 2004

Available online 11 September 2004

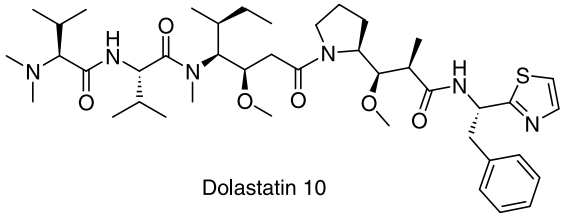
Abstract—The natural (2*R*,3*R*)-Boc-dolaproine and its unnatural (2*S*,3*S*) diastereoisomer were synthesized involving as key transformation the Ru(II)-promoted hydrogenation of the β-keto-α-methyl ester derived from (*S*)-*N*-Boc-proline. Interestingly, the asymmetric hydrogenation of this β-keto ester *N*-protected as an amine hydrochloride salt, provided the corresponding *anti* (2*S*,3*R*)- and (2*R*,3*S*)-β-hydroxy-α-methyl esters with significant level of selectivities through dynamic kinetic resolution.

1. Introduction

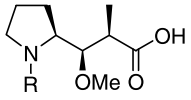
Naturally occurring (2*R*,3*R*)-dolaproine **1a** (Dap) is a key unit of dolastatin 10 originally isolated in 1987 from the Indian Ocean sea hare *Dolabella auricularia*. Dolastatin 10[1] is a potent inhibitor of microtubule assembly which displayed remarkable antineoplastic activity and is actually in phase II human cancer clinical trials (Fig. 1).[2,3]

Several groups have turned their attention towards the synthesis of dolaproine, which is the most complex unit of this marine natural product. The pioneering work of Pettit et al. was based on an aldol reaction of *N*-Boc-L-prolinal with the magnesium enolate of a chiral propionate leading to all four diastereoisomers in moderate yields and selectivities.[4,5] Subsequent efforts were focused on devising stereoselective and practical syntheses of dolaproine and its diastereoisomers. Shioiri et al. reported an efficient synthetic route to the synthesis of dolaproine[6–9] using Evans aldol methodology and condensation of *N*-Boc-L-prolinal with a chiral oxazolidinone in the presence of dibutylboron triflate, providing the desired *syn* compound with a complete diastereoselection.[10] Other syntheses of dolaproine involved aldol condensation with an achiral *Z*-boron enolate of thiophenyl propionate[11] or *Z*-crotylboronate[12] with moderate yields, while the use of benzyl propionate furnished a *syn*/*anti* mixture.[13] A convenient cobalt-mediated Reformatsky synthesis of Dap was also described by Pettit et al.[14] Another strategy was recently developed based on a Baylis–Hillman reaction between *N*-Boc-L-prolinal and methylacrylate which provided 91% of a diastereoisomeric mixture of *syn*/*anti* esters (83/17) after diastereoselective hydrogenation of the Baylis–Hillman adduct.[15]

Following our ongoing research devoted to the synthesis of natural products and industrially relevant molecules[16–19] using Ru-catalyzed hydrogenation reactions through dynamic kinetic resolution (DKR),[20–22] we have previously described a multigram-scale preparation of *anti* Boc-(2*S*,3*R*)-*iso*-dolaproine[23] with an excellent level of diastereoselectivity (d.e. 85%). This synthesis involving as key step the hydrogenation of the β-keto-α-methyl ester derived from the hydrochloride salt of (*S*)-proline turned out to be the first



Dolastatin 10



1a R = H, **dolaproine (Dap)**
1b R = Boc

Figure 1.

Keywords: Dolaproine; DKR; Asymmetric hydrogenation; Ruthenium.
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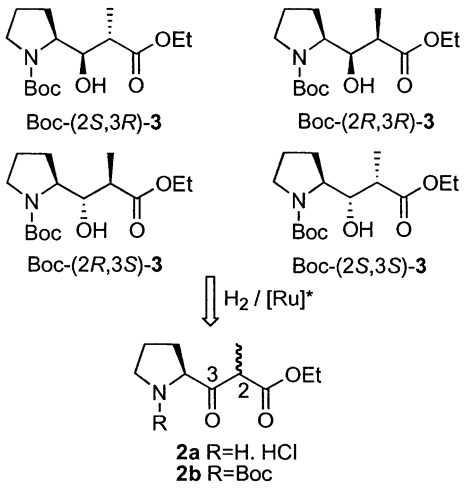
doi:10.1016/j.tet.2004.07.043



Scheme 1.

example of an efficient DKR of a β-keto ester α-substituted by an alkyl group, bearing at the γ-position a stereogenic center. We have also recently disclosed a general method for the stereoselective synthesis, from the same common intermediate, of *syn* and *anti* α-amino-β-hydroxy esters,[24,25] precursors of medically important compounds. Whereas the hydrogenation of α-amido-β-keto esters led to the *syn* adducts, DKR of these β-keto esters α-substituted by a $NH_2 \cdot HCl$ group provided the corresponding *anti* β-hydroxy esters with excellent selectivities.

In connection with our efforts to synthesize dolastatin 10 and its analogs required for biological trials, an attractive solution would be to develop a practical stereoselective route to all diastereoisomers of dolaproine from the same β-keto-α-methyl ester intermediate derived from (*S*)-proline. We thus anticipated that the nature of the *N*-protecting group of the (*S*)-proline fragment might influence the stereochemical outcome of the hydrogenation reaction.

In this paper, a simple and direct preparation of the naturally occurring Boc-(2*R*,3*R*)-dolaproine **1b** and its related diastereoisomers Boc-(2*S*,3*S*)-*iso*-dolaproine and Boc-(2*R*,3*S*)-*iso*-dolaproine is reported.

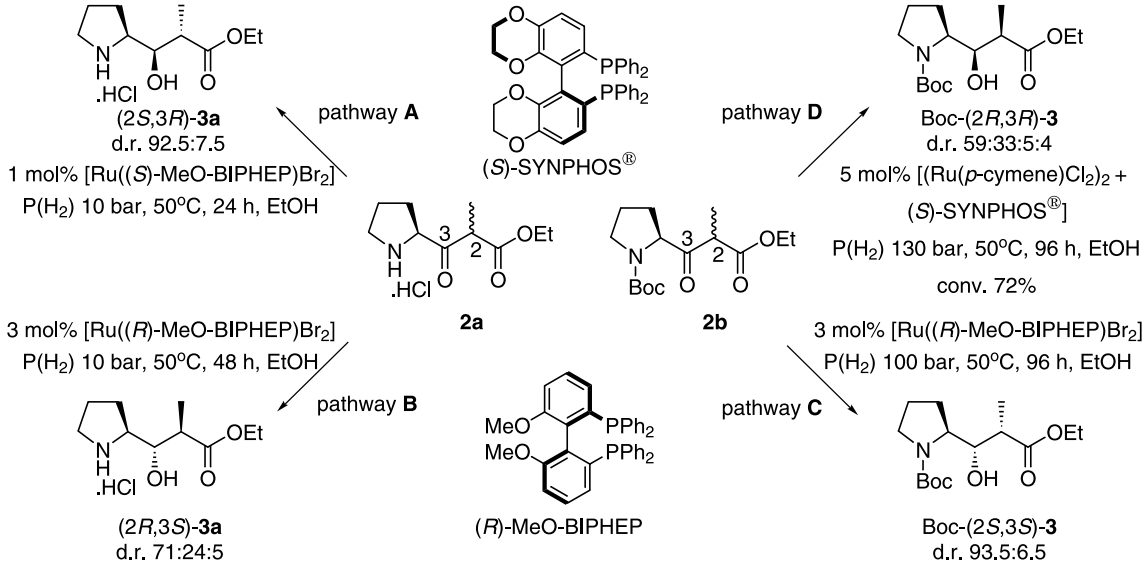
2. Results and discussion

The retrosynthetic approach for the required diastereoisomers of Boc-dolaproine **1b** was designed as follows (Scheme 1). Target compound **1b** would be obtained from the *N*-protected β-hydroxy esters **3**. The β-hydroxy-α-methyl esters **3** would be synthesized from the corresponding *N*-protected β-keto-α-methyl esters **2a** or **2b** by catalytic asymmetric hydrogenation.

The hydrogenation substrates **2a** and **2b** were easily prepared from the readily available (*S*)-*N*-Boc-proline.[23] The key hydrogenation was performed with the β-keto ester **2a** derived from the hydrochloride salt of (*S*)-proline (pathway **B**, Scheme 2). On the basis of our previous work (pathway **A**, Scheme 2),[23] we expected to obtain an *anti* diastereoselectivity.

The β-keto-α-methyl ester **2a** was hydrogenated under 10 bar at 50 °C for 48 h in ethanol with the in situ generated [Ru((*R*)-MeO-BIPHEP)Br_2] catalyst according to our convenient procedure.[26] Unlike the results described for the synthesis of Boc-(2*S*,3*R*)-*iso*-dolaproine involving the ligand of (*S*)-configuration,[23] we were surprised to find that the hydrogenation reaction with (*R*)-MeO-BIPHEP as ruthenium ligand proceeded rather slowly; 3 mol% of catalyst were required to ensure complete conversion. A moderate selectivity in favor of the *anti* β-hydroxy-α-methyl ester hydrochloride salt (2*R*,3*S*)-**3a** was observed. This lower diastereoselectivity could be the result of the following mismatched pair: chirality of the proline moiety and configuration of the ligand, as previously described in the literature.[27,28]

Spectroscopy analysis (^{1}H NMR in D_2O) of the crude hydrogenated product showed that the desired diastereoisomer (2*R*,3*S*)-**3a** was obtained in mixture with two other

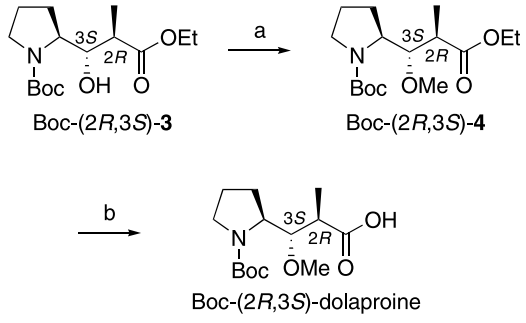


Scheme 2.

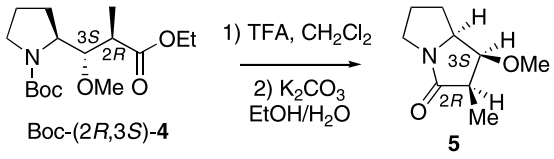
diastereoisomers, (2*S*,3*S*)-**3a** and (2*S*,3*R*)-**3a**, in a 71:24:5 diastereoisomeric ratio. This mixture was enriched up to 85:15 [(2*R*,3*S*)-**3a**:(2*S*,3*S*)-**3a**] by recrystallization in ethyl acetate.

Treatment of this mixture with Boc_2O in the presence of triethylamine afforded the corresponding *N*-protected compounds Boc-(2*R*,3*S*)-**3** and Boc-(2*S*,3*S*)-**3** which could not be separated by chromatography on silica gel. However the resulting 83:17 mixture was engaged in the *O*-methylation reaction with Me_3OBF_4 and proton sponge.[5] At this stage, optically pure *anti* Boc-(2*R*,3*S*)-**4** was isolated in 51% yield after flash chromatography (Scheme 3).

In order to confirm the stereochemistry of the diastereoisomer **3** obtained, Boc-(2*R*,3*S*)-**4** was treated with TFA and



Scheme 3. (a) Me_3OBF_4, proton sponge, CH_2Cl_2, 48 h, 51% yield. (b) NaOH, EtOH/H_2O, overnight.



Scheme 4.

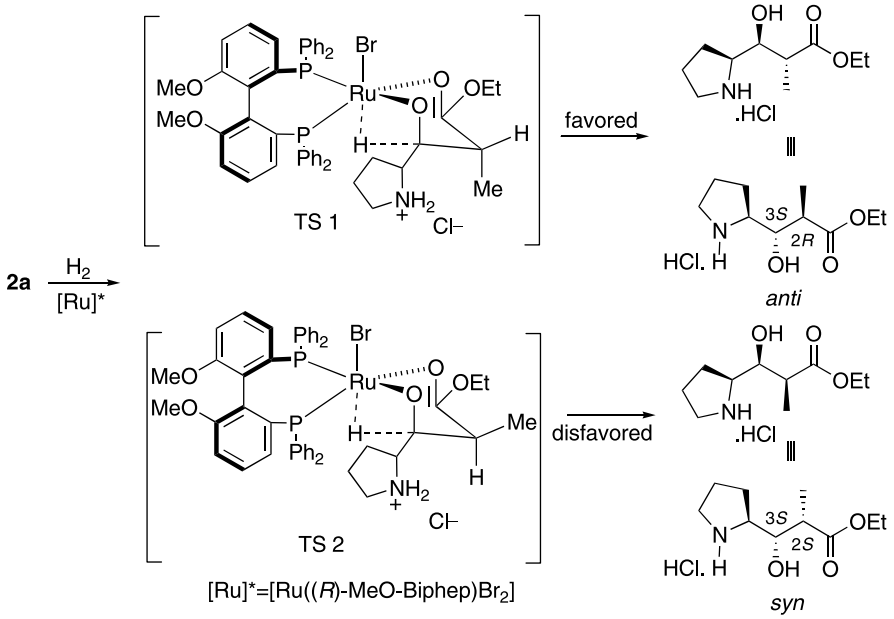
cyclized into the bicyclic lactam **5** by using potassium carbonate in a ethanol/water mixture (Scheme 4). The stereochemistry (2*R*,3*S*) of **3** was then assigned by NMR on the basis of NOE and COSY experiments.

The synthesis of *anti* Boc-(2*R*,3*S*)-*iso*-dolaproine was achieved by saponification of the ethyl ester function with sodium hydroxide (Scheme 3). Unfortunately, this reaction provided a mixture of the desired Boc-(2*R*,3*S*)-*iso*-dap and its isomerized diastereoisomer Boc-(2*S*,3*S*)-*iso*-dap.[29]

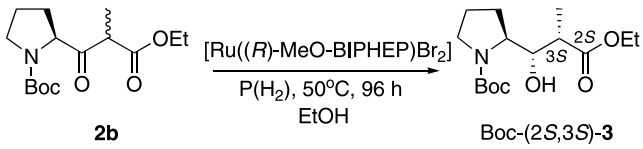
Although the origin of the *anti* diastereoselectivity is not clear at present, a chelated model could be speculated in which the substrate is coordinated to the metal by both its carbonyl oxygen functions (Scheme 5). Obviously, the chirality of (*R*)-MeO-BIPHEP as ruthenium ligand controls efficiently the stereofacial discrimination at the carbonyl function since the (3*S*) configuration is predominantly obtained, in agreement with the general sense of asymmetric hydrogenation.[30,31] Chair-like transition state TS1, where the methyl group adopts a pseudo-equatorial position is more favored than transition state TS2 exhibiting an axial methyl group. This could explain the predominant formation of the *anti* product.

Thus, we have demonstrated that the asymmetric Ru(II)-promoted hydrogenation reaction of the β-keto-α-methyl ester **2a** derived from the hydrochloride salt of (*S*)-proline provided the *anti* products (2*R*,3*S*)-**3** and (2*S*,3*R*)-**3**[23] as major diastereoisomers with moderate to good diastereoselectivities (41 and 85% d.e., respectively). The stereogenic center at the γ-position of the substrate seems to influence deeply the stereochemical outcome of the DKR.

According to our previous results obtained for the general synthesis of *syn* and *anti* α-amino-β-hydroxy esters,[24,25] we postulated that by simply changing the protecting group of the amine function of the proline moiety, the stereochemical course of the DKR of β-keto-α-methyl ester **2b** protected as



Scheme 5.



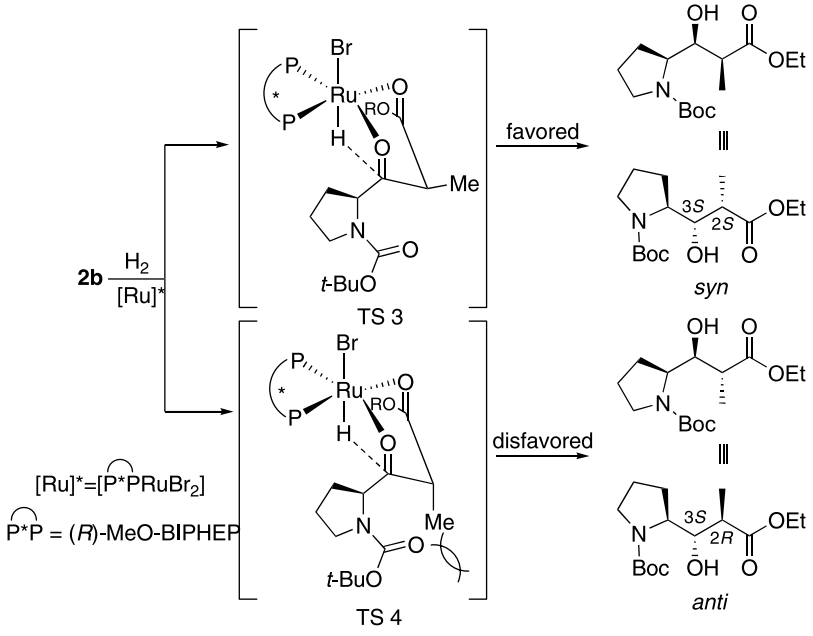
Scheme 6.

its *N*-Boc derivative would be in favor of the *syn* product as required for the dolaproine unit. In this context, we decided to examine the hydrogenation reaction of **2b** protected with a *tert*-butyloxycarbonyl group. Thus, we turned our attention to the synthesis of Boc-(2*R*,3*R*)-dolaproine **1b** (Dap) and its related diastereoisomer Boc-(2*S*,3*S*)-dolaproine.

The hydrogenation reaction of the β-keto ester derivative **2b** was first carried out in the presence of 1 mol% [Ru((*R*)-MeO-BIPHEP)Br_2] (Scheme 5, Table 1) at 50 °C under 95 bar of hydrogen pressure for 96 h. We were pleased to notice a remarkable reversal of the diastereoselectivity (entry 1). The *syn* (2*S*,3*S*) diastereoisomer was produced with high d.e. (entry 1, 83% d.e. on the crude product) but with a moderate conversion (66%). Thus we tried to optimize this reaction (Table 1). A complete conversion was ensured by increasing hydrogen pressure to 130 bar and the substrate/catalyst ratio to 5 and 3 mol% but unfortunately, lower chiral inductions were observed (entries 2 and 3, 72 and 77% d.e. on the crude product). Finally, the reaction was performed under 100 bar of hydrogen pressure at 50 °C with 3 mol%, affording the corresponding crude product Boc-(2*S*,3*S*)-**3** with an excellent control of the *syn* diastereoselectivity (entry 4, 87% d.e) (pathway **C**, Scheme 2). After chromatography on silica gel, Boc-(2*S*,3*S*)-**3** was isolated in 88% yield and 96% d.e. (Scheme 6).

The reversal of diastereoselectivity observed in the hydrogenation of the *N*-Boc protected proline derivative **2b** could be justified with the transition states proposed below (Scheme 7). As expected, the chirality of (*R*)-MeO-BIPHEP as ruthenium ligand controls the (3*S*) configuration of the product,[29,30] which was predominantly produced. Chair-like transition state TS3 having the methyl group and the bulky *N*-Boc-proline moiety in an 1,2 axial–equatorial relationship is rather favored compared to transition state TS4 where the methyl group adopts a pseudo-equatorial position. Even if at this stage we have no clear evidence, these suggested transition states TS3 and TS4 could explain the predominant formation of the *syn* Boc-(2*S*,3*S*)-**3**.

Considering the excellent asymmetric induction observed in the presence of [Ru((*R*)-MeO-BIPHEP)Br_2)], we focused our attention on the synthesis of the naturally occurring dolaproine (2*R*,3*R*)-Dap-**1b** which should be obtained by catalytic hydrogenation of **2b** with the opposite configuration of the ruthenium ligand ([Ru((*S*)-MeO-BIPHEP)Br_2)]). The hydrogenation reaction was conducted under 130 bar of hydrogen pressure at 50 °C for 96 h in ethanol with 5 mol% of catalyst. The reaction was not



Scheme 7.

Table 1. Asymmetric hydrogenation of compound **2b** using [Ru((*R*)-MeO-BIPHEP)Br_2]

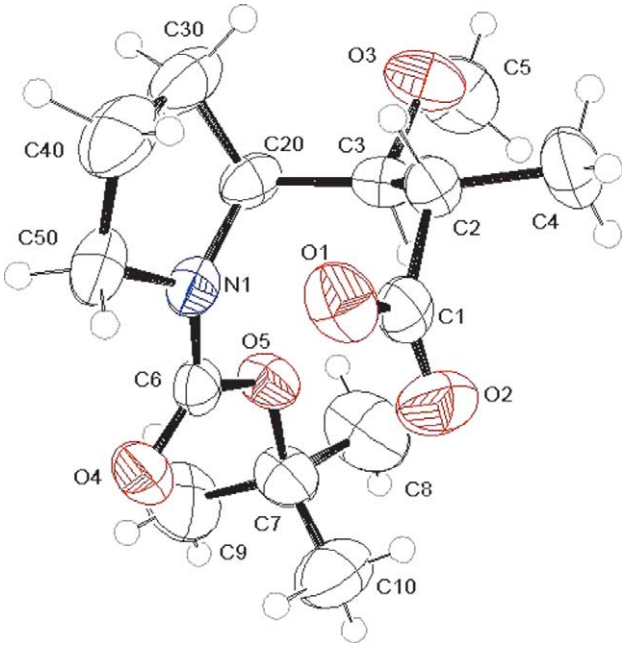
Entry	[Ru] (mol%)	P(H_2) (bar)	Conv. (%)	d.e. (2*S*,3*S*) (%)[a]
1	1	95	66	83
2	5	130	100	72
3	3	130	100	77
4	3	100	100	87

[a] d.e. determined on the crude product by ^{1}H NMR (300 MHz).

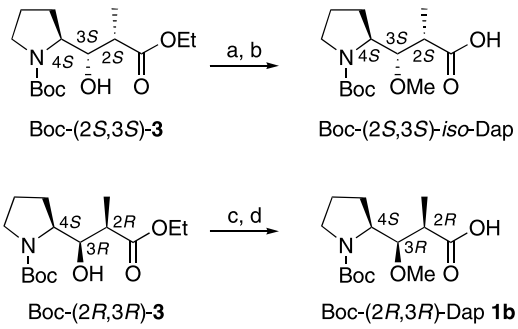
complete and the desired *syn* product Boc-(2*R*,3*R*)-**3** was obtained in mixture with the starting material **2b** (30–40%) and with the three other diastereoisomers. After flash chromatography, Boc-(2*R*,3*R*)-**3** was isolated in mixture with *anti* Boc-(2*S*,3*R*)-**3**. The conversion could be improved (up to 72%) and the proportion of the minor diastereoisomers *syn* Boc-(2*S*,3*S*)-**3** and *anti* Boc-(2*R*,3*S*)-**3** decreased (until 8%) by using the in situ generated catalyst simply prepared by mixing $[Ru(p\text{-cymene})Cl_2]_2$ and (*S*)-SYNPHOS® ligand recently developed in our group (pathway **D**, Scheme 2).[32] However *syn* Boc-(2*R*,3*R*)-**3** and *anti* Boc-(2*S*,3*R*)-**3** could not be separated and after chromatography on silica gel, a 2:1 d.r. was obtained in a 55% yield. The (3*R*) configuration is predominantly obtained suggesting that the ligand of (*S*) configuration controls quite well the enantiofacial discrimination; but in this case, the DKR is less efficient. Once again, the influence of the asymmetric center at the γ-position of the substrate is important for the control of selectivity.

Afterwards, the β-hydroxy esters Boc-(2*S*,3*S*)-**3** and Boc-(2*R*,3*R*)-**3** were subjected to the next synthetic steps: *O*-methylation and saponification (Scheme 9). The synthesis of *N*-Boc-*iso*-Dap (2*S*,3*S*)-**1** was achieved by *O*-methylation[5] followed by saponification of **6** to yield *N*-Boc-(2*S*,3*S*)-*iso*-Dap whose stereochemistry was unambiguously confirmed by X-ray analysis (Scheme 8).

After treatment of Boc-(2*R*,3*R*)-**3** with LHMDS in HMPA and MeOTf, the methoxy derivative Boc-(2*R*,3*R*) which led to the naturally occurring Boc-(2*R*,3*R*)-dolaproine **1b**, was isolated optically pure in a 45% yield after chromatography on silica gel, without any trace of *anti* (2*R*,3*S*) compound.[11]



Scheme 8. ORTEP drawing of Boc-(2*S*,3*S*)-*iso*-Dap (ellipsoïds, probability 50%)—selected bond distances (Å): C1–C2 = 1.518(5); C2–C4 = 1.538(6); C2–C3 = 1.529(5); C3–O3 = 1.427(4); O3–C5 = 1.378(5); C3–C20 = 1.542(5). Selected angles (°): C6–N1–C20 = 124.6(3); C6–N1–C50 = 119.4(3); C50–N1–C20 = 113.8(3); C5–O3–C3 = 115.6(3). Selected dihedral angles (calculated) (°): C30–C20–C3–O3 = −64.7; O3–C3–C2–C4 = −51.5. Nitrogen hybridization: (N1) (°) = 357.8.



Scheme 9. (a) Me_3OBF_4, proton sponge, CH_2Cl_2, rt, 24 h, 68% yield. (b) NaOH, EtOH/H_2O, 30 °C, 24 h, 73% yield. (c) (1) LHMDS, HMPA, THF, −78 °C, 25 min; (2) MeOTf, −20 °C, 15 min; 45% yield. (d) LiOH, EtOH/H_2O, overnight, 59% yield.

The absolute configuration of the *N*-Boc-Dap (2*R*,3*R*)-**1b** has been found to be identical to the previously synthesized compounds. All spectrometric data were in agreement with those reported in the literature (Scheme 9).[5]

3. Conclusions

In conclusion, we have succeeded in the synthesis of naturally occurring Boc-dolaproine **1b** and both (2*S*,3*S*)- and (2*R*,3*S*)-*iso*-dolaproine derivatives by developing a catalytic approach based on the ruthenium-promoted hydrogenation reaction via DKR as key transformation. The protecting group of the proline moiety turned out to play a crucial role in the stereochemical outcome of the asymmetric hydrogenation. The synthesis of dolastatin 10 and analogues is currently underway in our group and will be reported in due course.

4. Experimental

4.1. General methods

Dichloromethane was distilled from calcium hydride and tetrahydrofuran and diethyl ether from sodium-benzophenone. Acetone for the catalyst preparation was distilled over potassium carbonate. Other solvents were used without any purification. Triethylamine was distilled from potassium hydroxide. All air and/or water sensitive reactions were carried out under an argon atmosphere unless otherwise noted. ^1H NMR spectra were recorded on an Avance 300 at 300 MHz or an Avance 400 at 400 MHz; ^{13}C NMR spectra were recorded on an Avance 300 at 75 MHz or an Avance 400 at 100 MHz. Chemical shifts (δ) are reported in ppm downfield relative to internal Me_4Si. Coupling constants (*J*) are reported in Hz and refer to apparent peak multiplicities (recorded as s, singlet; d, doublet; t, triplet; q, quadruplet; qu, quintet; o, octet; m, multiplet; and br, broad). Mass spectra were determined on a Nermag R10-10C instrument. Ionization was obtained by chemical ionization with ammonia (DCI/NH_3) or by electrospray (on a API 3000 PE Sciex instrument). Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 589 nm (sodium lamp). GC analyses of compounds **3** were

performed on a Agilent 6850 series equipped with a HP01 column capillary column (30 m, ∅ 0.25 μm): 70–210 °C, 5 °C/min, flow: 4 mL/min (He).

4.2. Typical procedure for hydrogenation

(*S*)- or (*R*)-MeO-BIPHEP (0.011 mmol, 1.1 equiv, 6.4 mg) and (cod)Ru(2-methylallyl)$_2$ (0.01 mmol, 1 equiv, 3.2 mg) were placed in a 15 mL flask and 1 mL of anhydrous acetone previously degassed was added. A methanolic solution of HBr (0.022 mmol, 2.2 equiv, 141 μL of a 0.156 N solution prepared by added 48% aqueous HBr in degassed methanol) was added to the resulting suspension and the reaction mixture was stirred at room temperature for 30 min. The solvent was thoroughly evaporated under vacuum. The orange solid residue was used directly as catalyst (1 mol%) for the hydrogenation reaction. A solution (previously degassed) of the β-keto ester (1 mmol) in ethanol (1 mL) was added via canula to the catalyst and the reaction vessel was placed then in a 500 mL stainless steel autoclave, under argon. The autoclave was pressurized to the suitable pressure of hydrogen, heated at 50 °C and the reaction was allowed to proceed until completion. The crude reaction mixture was evaporated.

4.2.1. Ethyl (2*R*,3*S*,4*S*)-3-(2′-pyrrolidinyl)-3-hydroxy-2-methyl-propanoate hydrochloride (2*R*,3*S*)-3a. The title compound was obtained from ethyl (4*S*)-3-(2′-pyrrolidinyl)-3-oxo-2-methyl-propanoate hydrochloride[23] (2 mmol, 472 mg) according to the general procedure with the catalyst [Ru((*R*)-MeO-BIPHEP)Br$_2$] (0.06 mmol, 3 mol%) under 10 bar of hydrogen for 48 h. ^{1}H NMR analysis of the crude product (brown oil) showed a complete conversion and a 71:24:5 mixture of (2*R*,3*S*), (2*S*,3*S*) and (2*S*,3*R*) diastereoisomers (d.e. (2*R*,3*S*) 42%). After recrystallization in ethyl acetate, this mixture was enriched up to a 85:15 mixture of (2*R*,3*S*):(2*S*,3*S*) diastereoisomers. ^{1}H NMR (D_2O, 300 MHz, 24 °C): δ (major diastereoisomer) 4.10 (q, *J*=7.1 Hz, 2H), 3.80 (dd, *J*=5.3, 7.1 Hz, 1H), 3.72 (dq, *J*=7.3, 9.5 Hz, 1H), 3.24 (app t, 2H, *J*=7.3 Hz), 2.69 (dq, 1H, *J*=5.3, 7.1 Hz), 2.11–2.20 (m, 1H), 1.88–2.08 (m, 2H), 1.63–1.77 (m, 1H), 1.18 (t, *J*=7.1 Hz, 3H), 1.13 (d, *J*=7.1 Hz, 3H); δ (minor diastereoisomer) identical except 4.05 (m, 1H), 3.55 (app q, *J*=7.7 Hz, IH), 1.07 (d, *J*=7.1 Hz, 3H); ^{13}C NMR (D_2O, 75 MHz, 24 °C): δ (major diastereoisomer) 175.7, 72.3, 62.5, 62.0, 45.4, 43.3, 26.9, 23.4, 13.3, 13.1; δ (minor diastereoisomer) 176.3, 71.2, 62.9, 62.2, 45.2, 42.8, 26.8, 23.4, 13.3, 9.3; MS (DCI, NH_3): *m*/*z* 202 (100%, $[M+H]^+$).

4.2.2. Ethyl (2*R*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-hydroxy-2-methyl-propanoate Boc-(2*R*,3*S*)-3. Tri-ethylamine (1.2 mmol, 1.2 equiv, 0.17 mL) and di-*tert*-butyl dicarbonate (1.05 mmol, 1.05 equiv, 229 mg) were added to a stirred solution of ethyl (2*R*,3*S*,4*S*)-3-(2′-pyrrolidinyl)-3-hydroxy-2-methyl- propanoate hydrochloride (1 mmol, 238 mg) in ethanol (2 mL). After being stirred overnight at room temperature, the mixture was concentrated under reduced pressure. Tetrahydrofuran (10 mL) was added to the residue and the mixture was stirred for 15 min. The resulting precipitate was removed by filtration on a celite pad and washed with tetrahydrofuran. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography using cyclohexane–ethyl acetate (9:1) as eluent to give the *N*-Boc β-hydroxy ester (295 mg, 98% yield) as a pale yellow oil in a 83:17 mixture of (2*R*,3*S*):(2*S*,3*S*) diastereoisomers confirmed by GC analysis (t_R (2*R*,3*S*) 22.0, t_R (2*S*,3*S*) 22.7). ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 4.16 (q, *J*=7.1 Hz, 2H), 4.08 (app dt, *J*=3.6, 7.9 Hz, 1H), 3.56 (dd, *J*=3.8, 7.9 Hz, 1H), 3.50 (m, 1H), 3.30 (m, 1H), 2.65 (dq, *J*=3.8, 7.1 Hz, 1H), 1.60–2.05 (m, 4H), 1.46 (s, 9H), 1.28 (d, *J*=7.1 Hz, 3H), 1.26 (t, *J*=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ broad peaks (conformers) 174.2, 155, 80.3, 68.2, 60.4, 59.8, 47.2, 43.2, 28.4, 24.0, 23.5, 14.2; MS (DCI, NH_3): *m*/*z* 302 (100%, $[M+H]^+$), 263 (6%, $[M-C_4H_8+NH_4]^+$), 246 (25%, $[M-C_4H_8+H]^+$); $[\alpha]_D^{21}=-67.8$ (*c*=1.01, $CHCl_3$).

4.2.3. Ethyl (2*S*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-hydroxy-2-methyl-propanoate Boc-(2*S*,3*S*)-3. Obtained from ethyl (4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-oxo-2-methyl-propanoate[23] (2 mmol, 598 mg) according to the general procedure with the catalyst [Ru((*R*)-MeO-BIPHEP)Br$_2$] (0.03 mmol, 3 mol) under 100 bar of hydrogen for 96 h. ^{1}H NMR analysis of the crude product showed a complete conversion and a diastereoisomeric excess of 87%. Purification by silica gel column chromatography using cyclohexane–ethyl acetate (9:1) led to the β-hydroxy ester (435 mg, 88% yield) as a slightly yellow oil. ^{1}H NMR analysis showed a 98:2 mixture of (2*S*,3*S*):(2*R*,3*S*) diastereoisomers confirmed by GC analysis (t_R (2*S*,3*S*) 22.7, t_R (2*R*,3*S*) 22.0). ^{1}H ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 5.05 (br s, 1H, O*H*), 4.16 (dq, *J*=2.4, 7.2 Hz, 2H), 3.95 (m, 2H), 3.50 (m, 1H), 3.30 (ddd, *J*=5.5, 6.9, 10.9 Hz, 1H), 2.31 (dq, *J*=1.8, 6.9 Hz, 1H), 1.62–1.95 (m, 4H), 1.46 (s, 9H), 1.26 (t, *J*=7.2 Hz, 3H), 1.20 (d, *J*=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 174.4, 158.0, 80.8, 76.1, 60.6, 60.4, 47.1, 42.9, 28.4, 28.4, 24.1, 14.2, 8.9; MS (DCI, NH_3): *m*/*z* 302 (100%, $[M+H]^+$), 263 (7%, $[M-C_4H_8+NH_4]^+$), 246 (48%, $[M-C_4H_8+H]^+$); $[\alpha]_D^{21}=-76.2$ (*c*=0.97, $CHCl_3$).

4.2.4. Ethyl (2*R*,3*R*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-hydroxy-2-methyl-propanoate Boc-(2*R*,3*R*)-3. A solution of ethyl (4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-oxo-2-methyl-propanoate[23] (3 mmol, 897 mg) in absolute ethanol (6 mL) was degassed by three vacuum-argon cycles at room temperature and added via canula to the mixture (5 mol%) [Ru(*p*-cymene)Cl$_2$]$_2$ (0.075 mmol, 46 mg)+(*S*)-SYNPHOS® (0.165 mmol, 105 mg). The Schlenk vessel was then placed under argon in a 250 mL stainless steel autoclave. The argon atmosphere was replaced with hydrogen by three cycles of pressurizing and the pressure adjusted to 130 bar. The autoclave was heated at 50 °C and stirring was maintained for 96 h. After cooling, the reaction mixture was concentrated under reduced pressure to afford the crude β-hydroxy ester as a brown oil. ^{1}H NMR analysis showed a 72% conversion. The crude product was purified by silica gel column chromatography using cyclohexane–ethyl acetate (9:1) as eluent to give the β-hydroxy ester (500 mg, 55% yield) as a slightly yellow oil. GC analysis showed a 2:1 mixture of (2*R*,3*R*):(2*S*,3*R*) diastereoisomers (t_R (2*R*,3*R*) 21.8, t_R (2*S*,3*R*) 21.9). ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 5.01 (br s, 1H, O*H*), 4.14 (q, *J*=7.1 Hz, 2H), 3.99 (app t, *J*=4.9 Hz, 1H), 3.95

(m, 1H), 3.50 (m, 1H), 3.25 (m, 1H), 2.54 (m, 1H), 1.71–1.97 (m, 4H), 1.46 (s, 9H), 1.25(m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ broad peaks (conformers) 175.6, 155 (br), 79.9 (br), 73.8 (br), 60.5, 59.4, 47.3, 42.1, 28.5, 25.2, 24.3, 14.6, 14.1; MS (DCI, NH_3): *m/z* 302 (100%, $[M+H]^+$), 263 (4%, $[M-C_4H_8+NH_4]^+$), 246 (13%, $[M-C_4H_8+H]^+$); $[\alpha]_D^{21}=-47.7$ ($c=1.0$, $CHCl_3$).

4.2.5. Ethyl (2*R*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methyl-propanoate (2*R*,3*S*)-4. To a solution of ethyl (2*R*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-hydroxy-2-methyl-propanoate Boc-(2*R*,3*S*)-**3** (0.5 mmol, 150 mg) in dichloromethane (3 mL) was added 1,8-bis(dimethyl-amino)-naphtalene "proton sponge" (1 mmol, 2 equiv, 214 mg) followed by trimethyloxonium tetrafluoroborate (1.1 mmol, 2.2 equiv, 163 mg). The mixture was then stirred at room temperature for 24 h before a further addition of proton sponge (0.5 mmol, 1 equiv, 107 mg) and trimethyloxonium tetrafluoroborate (0.55 mmol, 1.1 equiv, 81 mg). The stirring was maintained for an additional 22 h before being filtered on a celite pad. The filtrate was washed successively with saturated aqueous citric acid and water, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether–ethyl acetate (9:1) as eluent to give the *N*-Boc β-methoxy ester (80 mg, 51% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 4.05–4.20 (m, 3H), 3.67 (m, 1H), 3.25–3.50 (m, 2H), 3.45 (s, 3H), 2.64 (dq, $J=2.6$, 7.0 Hz, 1H), 1.75–2.02 (m, 4H), 1.47 (m, 9H), 1.26 (t, $J=7.1$ Hz, 3H), 1.13 (br d, $J=7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 24 °C): δ broad peaks (conformers) 175.1, 154.5 (br), 84.0 (br), 79.2 (br), 60.2, 59.0 (br), 57.1, 47.5 (br), 42.8, 28.5, 29.6, 27.2, 14.6, 14.2; MS (DCI, NH_3): *m/z* 333 (3%, $[M+NH_4]^+$), 316 (100%, $[M+H]^+$), 277 (7%, $[M-C_4H_8+NH_4]^+$), 260 (21%, $[M-C_4H_8+H]^+$); $[\alpha]_D^{21}=-51.2$ ($c=0.16$, $CHCl_3$).

4.2.6. Ethyl (2*S*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methyl-propanoate (2*S*,3*S*)-4. To a solution of ethyl (2*S*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-hydroxy-2-methyl-propanoate Boc-(2*S*,3*S*)-**3** (1.20 mmol, 360 mg) in dichloromethane (5 mL) was added 1,8-bis(dimethyl-amino)-naphtalene 'proton sponge' (2.40 mmol, 2.0 equiv, 515 mg) followed by trimethyloxonium tetrafluoroborate (2.64 mmol, 2.2 equiv, 391 mg). The mixture was then stirred at room temperature for 24 h and then filtered over a celite pad and washed with dichloromethane. The filtrate was washed successively with saturated aqueous citric acid and water, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using cyclohexane–ethyl acetate (9:1) as eluent to give the *N*-Boc β-methoxy ester (257 mg, 68% yield) as a slightly yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 4.00–4.20 (m, 3H), 3.72–3.88 (m, 1H), 3.35–3.50 (m, 4H), 3.20 (m, 1H), 2.48 (m, 1H), 1.58–1.95 (m, 4H), 1.47 (m, 9H), 1.25 (t, $J=7.1$ Hz, 3H), 1.13 (d, $J=6.9$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 174.8, 154.1 (br), 82.1, 79.4, 60.4, 59.6, 58.0, 47.3 (br), 41.0, 28.4, 26.9 (br), 23.9, 14.2, 13.9; MS (DCI, NH_3): *m/z* 316 (100%, $[M+H]^+$), 277 (2%, $[M-C_4H_8+NH_4]^+$); 260 (21%, $[M-C_4H_8+H]^+$); $[\alpha]_D^{21}=-64.0$ ($c=0.25$, $CHCl_3$).

4.2.7. Ethyl (2*R*,3*R*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methyl-propanoate (2*R*,3*R*)-4. A solution of ethyl (2*R*,3*R*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-hydroxy-2-methyl-propanoate Boc-(2*R*,3*R*)-**3** (2 mmol, 602 mg) in tetrahydrofuran (6 mL) was added to a solution of LHMDS (1 M in THF, 2.8 mmol, 1.4 equiv, 2.8 mL) in HMPA (3.2 mmol, 1.6 equiv, 557 μL) and tetrahydrofuran (3.2 mL) at −78 °C. The stirring was maintained for 25 min at −78 °C before the addition at −20 °C of MeOTf (6.0 mmol, 3.0 equiv, 679 μL). The mixture was stirred at −20 °C for an additional 15 min. The reaction was then quenched with saturated aqueous ammonium chloride. After extraction with ethyl acetate, the organic layer was washed with saturated aqueous sodium chloride, dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using petroleum ether–ethyl acetate (9:1) as eluent to give the *N*-Boc β-methoxy ester (282 mg, 45% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 4.14 (br q, 2H, $J=7.1$ Hz), 3.70–3.95 (m, 2H), 3.53 (m, 1H), 3.41 (s, 3H), 3.22 (m, 1H), 2.47 (m, 1H), 1.80–2.05 (m, 3H), 1.65–1.77 (m, 1H), 1.49 (m, 9H), 1.25 (t, $J=7.1$ Hz, 3H), 1.23 (d, $J=7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 174.6, 154.4 (br), 83.4, 79.6 (br), 61.0 (br), 60.4, 59.6 (br), 46.6 (br), 43.1, 28.5, 26.2 (br), 24.0 (br), 14.2, 13.6; MS (DCI, NH_3): *m/z* 333 (7%, $[M+NH_4]^+$), 316 (100%, $[M+H]^+$), 277 (7%, $[M-C_4H_8+NH_4]^+$), 260 (34%, $[M-C_4H_8+H]^+$); $[\alpha]_D^{21}=-50.8$ ($c=1.2$, $CHCl_3$).

4.2.8. (2*R*,3*S*,4*S*)-hexahydro-3-methoxy-2-methyl-1-pyrrolizinone 5. To an ice-cooled solution of ethyl (2*R*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methyl-propanoate (0.16 mmol, 50 mg) in dichloromethane (3 mL) was added trifluoroacetic acid (500 μL). After 15 min at 0 °C, the mixture was stirred 1 h at room temperature. The solvent was thoroughly evaporated under vacuum. 3 mL of a mixture ethanol–water (1:2) was added to the residue and the resulting solution was cooled to 0 °C. Potassium carbonate (0.48 mmol, 3 equiv, 66 mg) was added portionwise and after 15 min at 0 °C, the stirring was maintained for 4 h at room temperature. The reaction mixture was then diluted and extracted with dichloromethane (3×25 mL) after the addition of saturated aqueous sodium chloride (10 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give the bicyclic lactam as a slightly yellow oil which crystallized upon standing. ^{1}H NMR ($CDCl_3$, 400 MHz, 24 °C): δ 3.86 (m, 1H), 3.75 (app t, $J=4.4$ Hz, 1H), 3.45 (m, 1H), 3.35 (s, 3H), 3.03 (m, 1H) 2.82 (m, 1H), 1.95–2.08 (m, 2H), 1.74–1.85 (m, 2H), 1.14 (d, $J=7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, 24 °C): δ 175.0, 81.2, 64.3, 59.7, 46.1, 41.2, 26.8, 23.7, 8.6.

4.2.9. (2*R*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methylpropanoic acid Boc-(2*R*,3*S*)-*iso*-dolaproine. To an ice-cooled solution of ethyl (2*R*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methyl-propanoate (0.6 mmol, 190 mg) in ethanol (5 mL) was added 1 N aqueous sodium hydroxide (1.80 mmol, 3 equiv, 1.8 mL). The mixture was stirred at 0 °C for 30 min then room temperature for 21 h. After further addition of 1 N aqueous sodium hydroxide

(2.43 mmol, 3 equiv, 2.43 mL), the mixture was stirred overnight at 30 °C. The resulting solution was acidified to pH 4 by adding 1 N aqueous hydrochloric acid and then extracted with a mixture ethyl acetate–toluene (1:1) (3× 30 mL). The organic extracts were washed with 1 M aqueous potassium hydrogen sulfate (20 mL) and saturated aqueous sodium chloride (30 mL), dried over sodium sulfate and concentrated under reduced pressure to give the crude product as a mixture of the desired (2*R*,3*S*)-Boc-*iso*-dolaproine and the isomerized stereoisomer (2*S*,3*S*)-Boc-*iso*-dolaproine. ^{1}H NMR ($CDCl_3$, 300 MHz, 24 °C): δ 4.11 (m, 1H), 3.50–3.72 (m, 1H), 3.47 (s, 3H), 3.30 (m, 1H), 2.68 (m, 1H), 1.80–1.97 (m, 2H), 1.60–1.72 (m, 2H), 1.47 (s, 9H), 1.24 (d, J=6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 178.3, 155.0 (br), 83.8, 79.3 (br), 60.0, 57.4, 47.0 (br), 42.0, 28.4, 27.1 (br), 23.5 (br), 15.4; MS (DCI, NH_3): *m/z* 288 (100%, $[M+H]^+$), 249 (11%, $[M-C_4H_8+NH_4]^+$), 232 (32%, $[M-C_4H_8+H]^+$); HRMS (DCI^+): *m/z* calcd for $C_{14}H_{26}O_5N$: 288.1811, found: 288.1809; $[\alpha]_D^{24}=-37.0$ (c=0.6, $CHCl_3$).

4.2.10. (2*S*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methylpropanoic acid Boc-(2*S*,3*S*)-*iso*-dolaproine. To an ice-cooled solution of ethyl (2*S*,3*S*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methyl-propanoate (0.81 mmol, 257 mg) in ethanol (5 mL) was added 1 N aqueous sodium hydroxyde (2.43 mmol, 3 equiv, 2.43 mL). The mixture was stirred at 0 °C for 30 min then heated at 30 °C overnight. After further addition of 1 N aqueous sodium hydroxide (2.43 mmol, 3 equiv, 2.43 mL), the mixture was stirred at 30 °C for an additional 6 h. The resulting solution was acidified to pH 4 by adding 1 N aqueous hydrochloric acid and then extracted with a mixture ethyl acetate–toluene (1:1) (3×30 mL). The organic extracts were washed with 1 M aqueous potassium hydrogen sulfate (20 mL) and saturated aqueous sodium chloride (30 mL), dried over sodium sulfate and concentrated under reduced pressure to give the crude product. The residue was purified by silica gel column chromatography using cyclohexane–ethyl acetate (7:3) as eluent to give the desired Boc-*iso*-dolaproine as an amorphous white powder (170 mg, 73% yield). ^{1}H NMR ($CDCl_3$, 400 MHz, 54 °C): δ 4.11 (m, 1H), 3.62 (m, 1H), 3.47 (s, 3H), 3.44–3.51 (m, 1H), 3.06 (m, 1H), 2.65 (m, 1H), 1.89–1.96 (m, 2H), 1.76–1.88 (m, 2H), 1.47 (s, 9H), 1.26 (d, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 175.9, 157.2 (br), 86.5, 81.0, 61.8, 58.8 (br), 48.3 (br), 44.2, 28.3, 26.9, 23.8, 13.9; MS (DCI, NH_3): *m/z* 288 (100%, $[M+H]^+$), 249 (10%, $[M-C_4H_8+NH_4]^+$), 232 (16%, $[M-C_4H_8+H]^+$); calcd for $C_{14}H_{25}NO_5$: C 58.52, H 8.77, N 4.87; found C 58.85, H 8.77, N 4.71; $[\alpha]_D^{24}=-57.0$ (c=0.75, $CHCl_3$).

4.2.11. (2*R*,3*R*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methylpropanoic acid Boc-(2*R*,3*R*)-dolaproine 1b. To an ice-cooled solution of ethyl (2*R*,3*R*,4*S*)-3-(*N*-*tert*-butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methyl-propanoate (0.78 mmol, 247 mg) in a mixture of ethanol (5 mL) and water (1 mL) was added lithium hydroxide monohydrate (2.35 mmol, 3 equiv, 99 mg). The mixture was then stirred overnight at room temperature. After evaporation of the solvent, the residue was diluted with dichloromethane and washed with water. The aqueous layer was acidified to pH 4 by adding 1 N aqueous hydrochloric acid and then extracted with ethyl acetate followed by dichloromethane. The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure to give the desired product as a colorless viscous oil (132 mg, 59% yield). ^{1}H NMR ($CDCl_3$, 400 MHz, 24 °C): δ 4.11 (m, 1H), 3.62 (m, 1H, 3.47 (s, 3H), 3.44–3.51 (m, 1H), 3.06 (m, 1H), 2.65 (m, 1H), 1.89–1.96 (m, 2H), 1.76–1.88 (m, 2H), 1.47 (s, 9H), 1.26 (d, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, 24 °C): δ 179.8 (br), 154.3 (br), 83.0, 79.9, 61.2, 59.4, 46.6, 42.8, 28.5, 26.1, 24.0, 13.5; MS (DCI, NH_3): *m/z* 305 (4%, $[M+NH_4]^+$), 288 (100%, $[M+H]^+$), 249 (14%, $[M-C_4H_8+NH_4]^+$), 232 (30%, $[M-C_4H_8+H]^+$); HRMS (DCI^+): *m/z* calcd for $C_{14}H_{26}O_5N$: 288.1811, found: 288.1804; $[\alpha]_D^{24}=-60.0$ (c=1.03, MeOH).

Acknowledgements

We thank Dr. R. Schmid and Dr. M. Scalone (Hoffmann-La Roche) for samples of (*R*)- and (*S*)-MeO-BIPHEP=(*S*)-(−)-6,6′-dimethoxy-2,2′-bis(diphenylphosphino)-1,1′-biphenyl. A fellowship from C.N.R.S./D.G.A. (C. Mordant) is gratefully acknowledged. Dr. S. Reymond is grateful to C.N.R.S. for a post-doctoral fellowship.

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