Transannular rearrangement of activated 2,5-diketopiperazines: a key route to original scaffolds†

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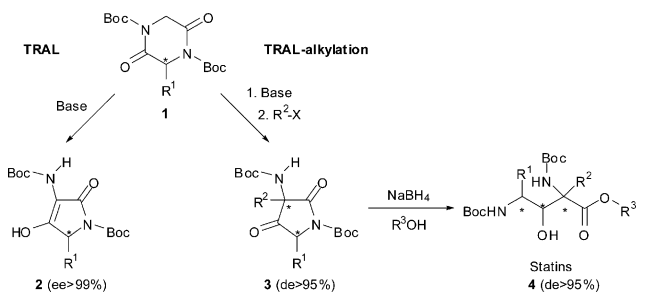
An efficient and original stereocontrolled transannular rearrangement starting from activated 2,5-diketopiperazines has been developed, an opportunity for the medicinal chemistry field, which requests access to novel biological scaffolds. This powerful ring contraction, which can be related to a stereoselective aza-version of the Chan rearrangement, allows for example the one-step synthesis of various tetramic acids, access to 2-disubstituted statins, or the synthesis of relevant lactam-constrained dipeptide mimetics using a TRAL–RCM sequence.

Introduction

Access to new therapeutic entities depends greatly on the discovery of original and pertinent scaffolds, connected with the development of innovative synthetic reactions. In the perpetual quest for pioneering compounds, we recently described an unprecedented ring contraction reaction. The transannular rearrangement of activated lactams (TRAL) leads to 4-hydroxy-3-pyrrolin-2-ones **2** starting from suitable Boc-activated 2,5-diketopiperazines **1** (Scheme 1).[1] This powerful rearrangement could be seen as a new intramolecular N→C acyl migration reaction of cyclic imides. It can be related to a highly stereocontrolled aza-version of the Chan rearrangement,[2] or to the interesting reaction of acyclic imides described by Hamada *et al*.[3]



Scheme 1 TRAL and TRAL-alkylation. Access to statins.

By adding an alkylating agent during the course of the TRAL, bis-Boc *cyclo*-[Gly-X] **1** can be easily converted into its dialkylated pyrrolidine-2,4-dione **3** in an exceptionally diastereoselective manner (TRAL-alkylation, Scheme 1). This regioselective ring contraction allows then the one-step synthesis of various substituted pyrrolidine-2,4-diones or tetramic acids, key patterns founded in several biological compounds.[4] Moreover, the first successful application of the TRAL leads to a highly selective synthesis of various novel 2-disubstituted statins **4**.[5,6]

After a full account of our results on the TRAL/TRAL-alkylation, including a debate on various activating groups of the 2,5-diketopiperazines (DKPs), we will extend the discussion to the postulated mechanism and then report on original applications of TRAL, such as the asymmetric synthesis of original lactam-constrained dipeptide mimetics as a key route to promising heterocyclic scaffolds.

Results and discussion

The transannular rearrangement of activated lactams (TRAL): a serendipitous finding

Stereoselective ring contraction of DKPs into 3-aminotetramates

While our efforts were initially devoted to the stereoselective 3- or 6-alkylation of bis-(*N*-*tert*-butoxycarbonyl)-DKPs (bis-Boc-DKPs), by taking advantage of the electrophilicity of such substituted lactams, we made an unexpected observation. Instead of displaying a predictable protecting group character, under certain basic conditions, the two Boc moieties acted as electron withdrawing activators, allowing the unusual transformation of symmetrical and unsymmetrical bis-Boc-DKPs **1** into the corresponding 3-aminopyrrolidine-2,4-diones **2** (Scheme 1).

A preliminary study has concentrated on the reaction with diprotected bis-Boc-DKPs **5a–f**, in the presence of *t*-BuOK (Table 1).

Contradictorily to the few examples described in the literature concerning the reactions on Boc-protected DKPs under basic conditions,[7,8] we highlighted a new kind of reactivity. According to chiral HPLC analyses, ^{1}H NMR and ^{13}C NMR studies, we observed that the keto–enolic equilibrium of pyrrolidine-2,4-diones was always shifted towards the enol formation. We noticed a totally regioselective ring contraction which allows the exclusion from the ring system of the Boc-*N*1 of the DKPs, leading to the formation of the corresponding aminotetramates **6a–f** in good yields with

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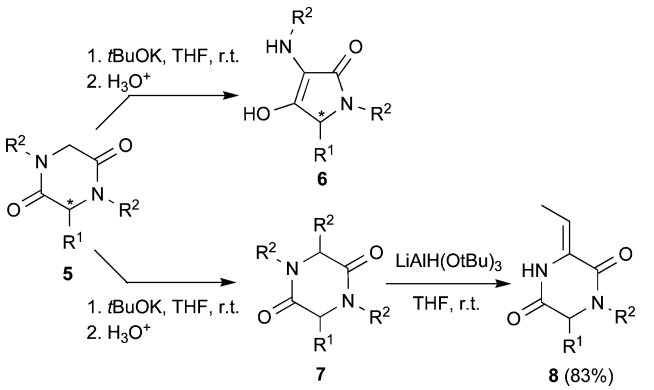
† CCDC reference number 643845. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b810352f

Table 1 Stereocontrolled ring contraction of activated DKPs



Entry	5	R^1	R^2	6/7	Yield[a] (%)	ee[b] (%)
1	**5a**	H	Boc	**6a**	72	—
2	**5b**	Me (*S*)	Boc	**6b**	60	>99
3	**5c**	Me (*R*)	Boc	**6c**	64	>99
4	**5d**	*i*Pr (*S*)	Boc	**6d**	82	>99
5	**5e**	*i*Pr (*R*)	Boc	**6e**	84	>99
6	**5f**	*s*Bu (*S*)	Boc	**6f**	71	>95
7	**5g**	*i*Pr (*S*)	Z	**6g**	0	—
8	**5h**	H	Bz	**6h**	69	—
9	**5i**	*i*Pr (*S*)	Bz	**6i**	98	87
10	**5j**	*i*Pr (*R*)	Bz	**6j**	98	87
11	**5k**	H	Ac	**7**	37	—

[a] Yield of product isolated by flash chromatography. [b] The ee values were determined by HPLC on a chiral phase.

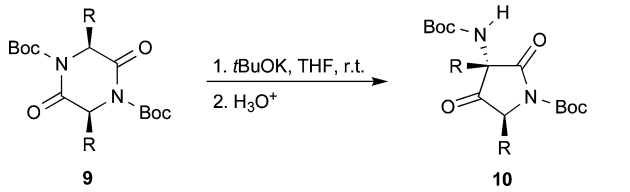
excellent enantioselectivities and with absolute retention of the initial configuration.

The examination of the feasibility of this serendipitous rearrangement was then extended to other conventional N-protecting groups that could be perceived as lactamic activators of the TRAL. While no reaction was detected with a bis-Z-DKP (entry 7, Table 1), the reaction of bis-Bz-DKPs occurred with higher yields but lower stereoselectivity, contrasting with the exceptional enantioselectivity described for the bis-Boc-DKPs (entries 8–10, Table 1). This tiny fall in stereoselectivity could be explained by the increased facility of racemisation of the bis-Bz-DKPs in alkaline media.

Interestingly, when we investigated the switch to bis-Ac-DKP **5k**, the tris-acetylated DKP **7** was produced in moderate yield with no trace of the corresponding tetramate (entry 11, Table 1). Ascribing this to an intermolecular acetyl migration, since unprotected DKP was simultaneously generated, we then exploited this peculiarity for the synthesis of an interesting scaffold. The reduction of the DKP **7** using $LiAlH(OtBu)_3$ allowed us access to the dehydro product **8**, in good yield, in a Perkin-like elimination with concomitant cleavage of the neighboring acetyl group. The *Z*-stereochemistry of this compound was established using ^1H NMR spectra by comparison with previously described analyses.[9]

Further applications of the TRAL to other symmetrical DKPs, such as di-protected *cyclo*-[X-X] (X = Ala, Val, Glu(OMe)), provide original substituted pyrrolidine-2,4-diones, in which the two alkyl chains belong to the same half-space of the heterocyclic moiety (Table 2).

Table 2 TRAL on symmetrical DKPs

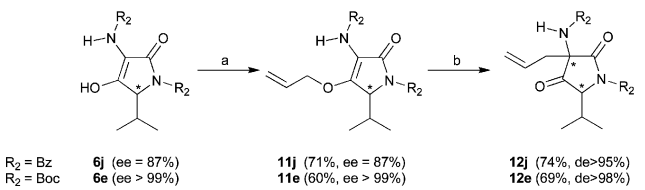


Entry	9	R	10	Yield[a] (%)	de[b] (%)
1	**9a**	Me (*S*)	**10a**	66	67
2	**9b**	*i*Pr (*S*)	**10b**	68	>95
3	**9c**	$MeO_2C(CH_2)$ (*S*)	**10c**	29	>95

[a] Yield of product isolated by flash chromatography. [b] The de values were determined by HPLC of the crude product.

Claisen-like rearrangement applied to the TRAL products (obtained from unsymmetrical DKPs)

With the scope of the TRAL on unsymmetrical DKPs established, the synthetic value of the tetramate adducts was then investigated. The asymmetric Claisen-like rearrangement described for 3-*O*-allyl(*iso*propylidene)ascorbate[10] was successfully transposed to the bis-Bz-pyrrolidine-2,4-dione **6j** and to the bis-Boc-pyrrolidine-2,4-dione **6e**. After an appropriate *O*-allylation, derivatives **11j** and **11e** followed a sigmatropic rearrangement to yield **12j** and **12e** in a stereocontrolled manner (Scheme 2).



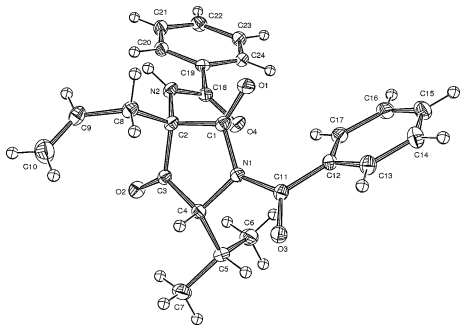
Scheme 2 Claisen-like rearrangement. *Reagents and conditions*: (a) KOH, DMSO, CH_2=$CHCH_2Br$; (b) microwave irradiation, toluene–DMSO, 170 °C, 30 min.

The stereochemistry of this Claisen-like rearrangement was unambiguously determined by X-ray diffraction crystal analysis of the major compound **12j** enantioenriched by recrystallization (Scheme 3).‡

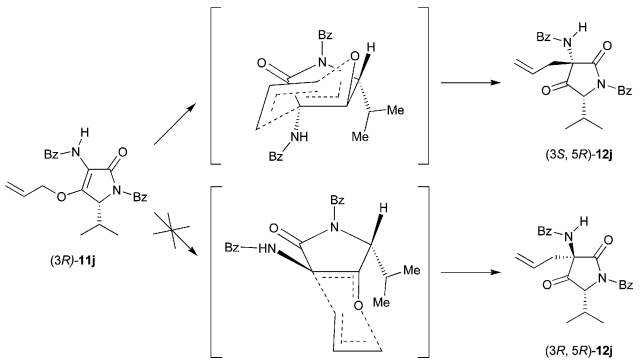
The high diastereoselectivity of this sigmatropic rearrangement could be easily explained by the structural parameters of the Zimmermann–Traxler chair transition state, as illustrated by Scheme 4.

In agreement with our preliminary studies on TRAL, benzoyl groups also appear to be a suitable alternative to Boc activating groups here.

‡ $C_{24}H_{24}O_4N_2$, *M*r = 404.45, orthorhombic, $P2_12_12_1$, *a* = 10.4911(5), *b* = 12.2289(6), *c* = 16.1319(7) Å, *V* = 2069.6(2) Å^3, *Z* = 4, D_X = 1.298 Mg.m^{-3}, λ(Mo Kα) = 0.71073 Å, μ = 0.89 cm^{-1}, F(000) = 856, *T* = 110(1) K. CCDC 643845. These data can also be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.uk/data_request/cif.



Scheme 3 X-Ray analysis of (3*S*,5*R*)-**12j**.



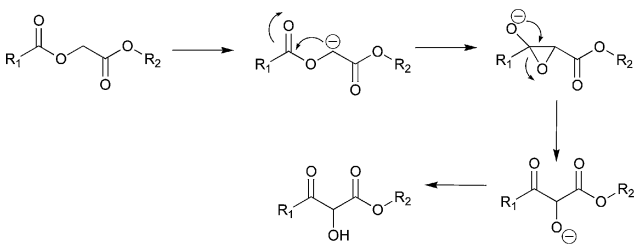
Scheme 4 Zimmermann–Traxler chair transition state.

Stereoselective ring contraction of DKPs in the presence of an alkylating agent: the TRAL-alkylation

To improve the access to more functionalized tetramates, we have already described a viable route for the relevant regioselective and stereoselective ring contraction of DKPs into pyrrolidine-2,4-diones in the presence of an alkylating agent. By using symmetrical or unsymmetrical DKPs, we could obtain a range of derivatives bearing the two side chains R_1 and R_2 on the same face of the heterocyclic ring (Table 3).

Towards a plausible mechanism to explain the stereoselectivity of the TRAL

The transannular rearrangement of activated lactams (TRAL), an intramolecular acylation of an imide enolate, could be related to the Dieckmann and Gabriel–Colman reactions or to the early step of the Dakin–West reaction. However, a better match could be made with the Chan reaction,[2] a rearrangement of an acyloxyacetate to a 2-hydroxy-3-keto-ester in the presence of a strong base (Scheme 5). Its aza-version has been developed on acyclic imides by Hamada *et al.*[3] and extended to biological hits by Wipf and Methot,[11] and White *et al.*,[12,13] as illustrated by the Holton Taxol total synthesis.[14]

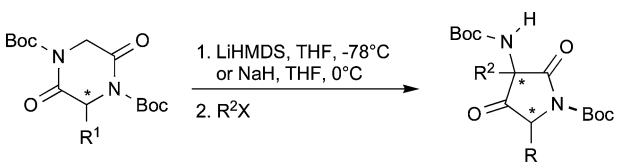


Scheme 5 The Chan rearrangement.

As suggested by Wipf and co-workers, only the *s*-cis conformation of the ester and the tertiary amide of the incriminated imide moiety is able to undergo the Chan rearrangement. A transposition of this interpretation could allow us to connect the success of the TRAL to the unique presence of the *s*-cis conformation, since bis-Boc-DKPs could be likened to constrained cyclic systems of two imides.

Concerning the mechanism of the TRAL, we anticipated that the TRAL of activated DKPs could sensibly follow the Chan–Hamada reaction (Scheme 6). We proposed that after a suitable deprotonation of the activated DKP under basic conditions, the kinetic enolate would be formed. The transannular attack of the enolate, and nucleophilic acyl substitution with the adjacent carbonyl of the imide group could afford an aziridine intermediate,

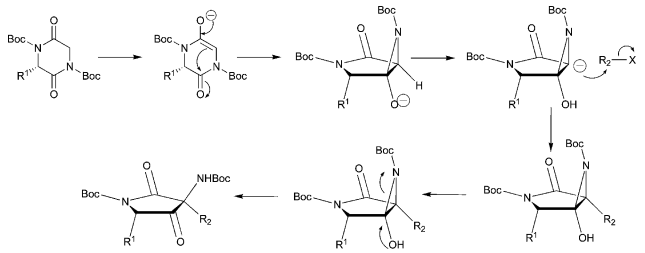
Table 3 TRAL-alkylation of unsymmetrical and symmetrical DKPs



5 **13**

Entry	**5**	R^1	R^2X	R	**13**	Yield[a] (%)	de[b] (%)
1	**5a**	H	CH_2=$CHCH_2Br$	$=R^2$	**13a**	62	>95
2	**5a**	H	BnBr	$=R^2$	**13b**	57	>95
3	**5e**	*i*Pr (*R*)	CH_3I	$=R^1$	**13c**	60	>95
4	**5e**	*i*Pr (*R*)	BnBr	$=R^1$	**13d**	72	>95
5	**5e**	*i*Pr (*R*)	EtO_2CCH_2I	$=R^1$	**13e**	69	>95
6	**5e**	*i*Pr (*R*)	CH_2=$CHCH_2Br$	$=R^1$	**13f**	76	>99
7	**5e**	*i*Pr (*R*)	$(CH_3)_2C$=$CHCH_2Br$	$=R^1$	**13g**	84	>95
8	**5f**	*i*Bu (*S*)	CH_2=$CHCH_2Br$	$=R^1$	**13h**	68	>95

[a] Yield of product isolated by flash chromatography. [b] The ^{13}C NMR spectra gave only one set of peaks.



Scheme 6 Postulated mechanism for the TRAL, by analogy with the Chan reaction.

in accordance with the oxirane formation described for the Chan reaction.

To explain the exceptional stereoselectivity of the TRAL, we could postulate that the aziridine ring would be positioned on the less bulky half-space rather than on the face containing the side chain R^1. Prototropy on the oxanion could lead to the anionic intermediate shown. In the presence of an alkylating reagent such as R^2–X, we have anticipated that the constrained ring system could hinder the attack of the sp^3 carbanion on the face where the Boc-aziridine moiety is located. The electrophile could then only add to the open half-space of the heterocycle, where the R^1 group is pointed away from the Boc-aziridine moiety. In the last step, the opening of the aziridine affords the resulting bis-Boc 3-aminopyrrolidine-2,4-dione or its enolic form. The possibility of immediate ring opening of the *in situ* formed aziridine intermediate could be also considered. This opening could be induced by the alkoxide anion, followed by prototropy to the nitrogen anion, affording an anionic intermediate which could attack the electrophile R^2–X. Taking into account the high reactivity of 2-oxyaziridines, the ring opening of the proposed 2-hydroxyaziridine intermediate in a final stage of the process is less likely.[15]

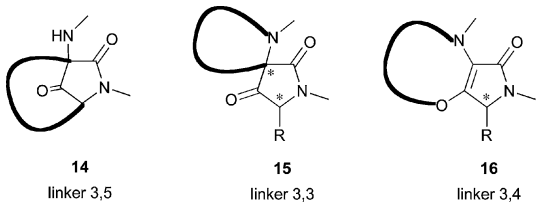
TRAL: a key route to promising scaffolds

Besides the first described application of the TRAL leading to the synthesis of statin analogues, we describe here an original access to promising heterocyclic scaffolds, using a tandem TRAL–metathesis approach.

Asymmetric synthesis of original lactam-constrained dipeptide mimetics

The concept of conformational constraint has emerged as the favourite method in medicinal chemistry of "freezing" the bioactive conformation of the initial peptide in order to optimize its activity, its receptor selectivity or the duration of its action.[16–26] Since the lactam-bridged dipeptides described by Freidinger *et al.* have been well recognized to be a significant type of conformational constraint in peptides[27,28] and since the ring-closing metathesis reaction has been shown to be a powerful method of accessing rigidified dipeptides of biological interest,[29–32] we chose to design a new and efficient method leading to original lactam-constrained dipeptide mimetics.

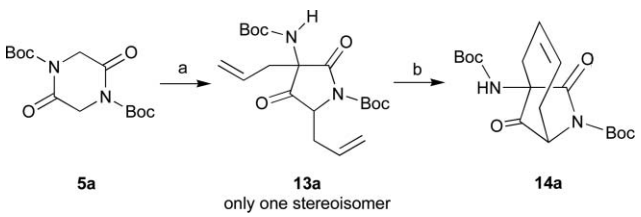
Using a highly stereoselective chemical sequence, TRAL followed by a ring-closing metathesis reaction (RCM), we have been able to access unprecedented heterocyclic scaffolds **14**–**16** (Scheme 7), that could be received as dipeptide mimetics.



Scheme 7 Lactam-constrained dipeptide mimetics.

Furthermore, the presence of a quaternary stereogenic carbon center enhances the significance of these bicyclic derivatives, regarding the fact that aza-cyclic α-aminoacids with quaternary stereocenters are part of biologically active natural products with therapeutic potential,[33–35] and are useful building blocks for natural product synthesis and enantioselective syntheses.[36–40]

In order to add more constraints on the pyrrolidine-2,4-dione moieties, we first imagined linking the side chains of the dipeptide mimetic, taking the opportunity given by the TRAL to choose their spatial arrangement. First of all, as we already demonstrated, the bis-Boc *cyclo*-[Gly-Gly] **5a** can be easily converted into its dialkylated pyrrolidine-2,4-dione **13a** in a diastereoselective manner (Scheme 8). With both allyl chains being in the same half-space and properly positioned for cyclization, the use of a Grubbs' catalyst II in the second step leads to the over-constrained derivative **14a** in good yield.



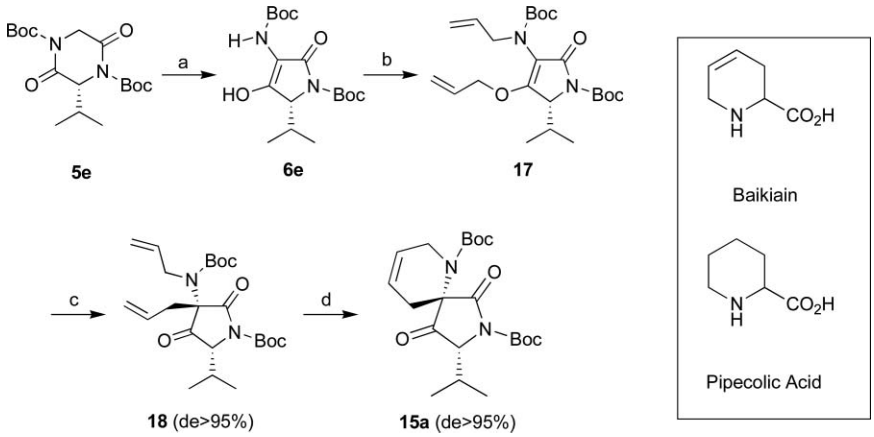
Scheme 8 Synthesis of *bicyclo*-compound **14a** starting from bis-Boc *cyclo*-[Gly-Gly]. *Reagents and conditions*: (a) (i) LiHMDS, −78 °C, THF (ii) CH_2=$CHCH_2Br$, 62%; (b) 2% mol Grubbs' catalyst II, CH_2Cl_2, r.t., 84%. About **14a**: the ^{13}C NMR spectrum of the crude material gave only one set of peaks.

In the quest for novel heterocyclic scaffolds and encouraged by the efficiency of this pioneering ring-closing metathesis on pyrrolidine-2,4-dione derivatives, we decided to expand our strategy to the synthesis of *spiro*-derivatives.

By taking advantage of the potential for high stereoselectivity of one of our previously reported synthetic sequences, the TRAL and *O*-allylation followed by a Claisen-like rearrangement, we already knew how to access 3-allyl-3-aminopyrrolidine-2,4-dione **12e** from bis-Boc *cyclo*-[Gly-D-Val] **5e** (Scheme 2).

Taking a bet on this totally diastereoselective sequence, we were then able to transpose it to the *O*,*N*-diallyl derivative **17**, which could be accessed from the same aminotetramate intermediate **6e** by using two equivalents of base and allyl bromide. The sigmatropic rearrangement provided the new *C*,*N*-diallyl **18** in good yield in a stereocontrolled manner. This reaction was carried out under microwave conditions, which appeared to be more efficient than thermal conditions.

A suitable intramolecular cyclization by ring-closing metathesis of the pyrrolidine-2,4-dione **18**, allowed the new stereoselective

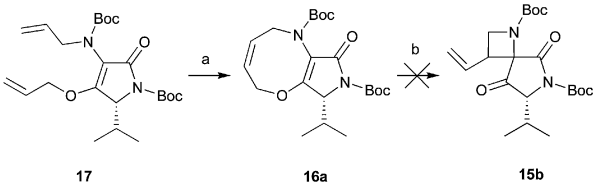


Scheme 9 TRAL and *O*-allylation followed by a Claisen-like rearrangement. *Reagents and conditions*: (a) *t*BuOK, THF, r.t., 84%; (b) KOH (2.0 equiv.), DMSO, CH_2=$CHCH_2Br$ (2.0 equiv.), 76%; (c) microwave irradiation, toluene–DMSO, 170 °C, 30 min, 73%; (d) 2% mol Grubbs' catalyst II, DCM, r.t., 88%. About **15a**: the ^{13}C NMR spectrum of the crude material gave only one set of peaks.

construction of the innovative [5 + 6] *spiro*-derivative **15a** in excellent yield (Scheme 9).

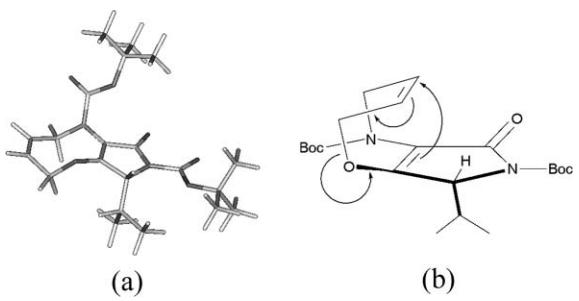
This unprecedented *spiro*-scaffold could be classified as a significant lactam-constrained dipeptide mimetic. In addition it could be also considered a more complex derivative of Baikiain, a cyclic α-amino acid isolated from the heartwood of Rhodesian teak (*Baikiaea plurijuga*).[41] This interesting natural compound is an unsaturated derivative of pipecolic acid, which is a non-proteinogenic amino acid present in pharmacologically active molecules such as immunosupressors or antitumor antibiotics.[42]

Finally, regarding the fact that using RCM to synthesize an eight-membered cycle is still challenging,[43,44] we performed the cyclization starting from the intermediate compound **16a**, to build the [5 + 4] *spiro*-derivative **15b**, another lactam-constrained dipeptide mimetic (Scheme 10). We were delighted to observe that the aminotetramate **17** was easily converted into the novel *bicyclo*-derivative **16a**, in good yield, probably helped by the steric constraints induced by the *N*-Boc group. This optically active compound **16a** can be considered as an interesting *bicyclo*- and dehydro- quaternary dipeptide mimetic.



Scheme 10 Synthesis of a [5 + 4] *spiro*-derivative. *Reagents and conditions*: (a) 2% mol Grubbs' catalyst II, CH_2Cl_2, r.t., 78%; (b) microwave irradiation, toluene–DMSO, 170 °C, 30 min.

Interestingly, under microwaves or thermal conditions, the sigmatropic rearrangement of **16a** was unsuccesful, leading to a partial cleavage of the Boc protecting group. In order to give an explanation, we first postulated two ring-conformations for **16a**, the chair-like and boat-like conformations. A careful examination of the ^1H NMR spectrum of the eight-membered ring part of the cyclic system, showed unambiguously that the allylic methylene protons on the nitrogen side possess anisochrony, exhibited as a significant splitting of signals ($\Delta\delta$ = 1.42 ppm). This allowed us to conclude on a chair-like favorite conformation. This observation was also confirmed by molecular modelling studies on **16a** (Scheme 11a).[45] We then had to admit that the boat-like conformer was critical for the transannular reaction (Scheme 11b).



Scheme 11 (a) The predicted lower energy conformation of **16a**: the chair-like favorite conformation observed by molecular modelling studies and ^1H NMR; (b) the boat-like conformer probably crucial for the transannular Claisen rearrangement reaction.

Conclusions

In conclusion, we have devised a powerful method for accessing new lactam-constrained dipeptide mimetics, new chemical entities that could be of broad interest in the quest for original scaffolds for drug discovery. The success of this strategy is closely linked to the access to suitable building blocks for the ring-closing metathesis, which can only be obtained by the highly stereocontrolled TRAL. The association of the TRAL and an unprecedented ring-closing metathesis on pyrrolidine-2,4-dione derivatives provided lactam-constrained dipeptide mimetics in good yields with remarkable stereoselectivity. We believe that this study will offer a strong incentive for the construction of larger or structurally modified dipeptide mimetics and potentially novel biological hits.

Experimental

General procedures

All solvents were dried and freshly distilled prior to use. TLC was performed with Merck-Kieselgel 60 F_{254} plates, and spots were visualized with UV light and/or by staining with ninhydrin solution followed by heating. Flash chromatography was performed on Merck-Kieselgel 60 (230–400 mesh). Melting points were recorded on Buchi 510 melting apparatus. Optical rotations were measured with a 1 cm cell (concentration c given in g 100mL^{-1}solvent) on a Perkin Elmer Polarimeter at 20 °C with a sodium lamp (589 nm). HPLC analyses were performed on a Waters-Millennium (column 250 × 4.6 mm Nucleosil C18 5 µ, detection UV). High resolution mass spectra (HRMS) were obtained on a JEOL JMS-SX-102 high resolution magnetic sector mass spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with Bruker 200 MHz, Bruker AC250 MHz, Bruker Advance 300 MHz or Bruker A DRX 400 MHz spectrometers. Chemicals shifts are reported in δ relative to an internal standard of residual chloroform ($\delta = 7.26$ for ^{1}H NMR and 77.16 for ^{13}C NMR) or DMSO-d_6 ($\delta = 2.50$ for ^{1}H NMR and 39.52 for ^{13}C NMR). The reported ^{1}H NMR signals were assigned using standard 2D NMR techniques or by direct comparison to the ^{1}H NMR spectra of the corresponding starting materials. The reported ^{13}C NMR signals were assigned using DEPT-135 and HMQC techniques or by direct comparison of the ^{13}C NMR spectra of the corresponding starting materials.

1,4-Di(benzoyl)-piperazine-2,5-dione 5h

Typical procedure for the benzoylation of DKP. A solution of piperazine-2,5-dione (0.198 g, 1.74 mmol) and benzoic anhydride (1.572 g, 6.95 mmol) in toluene (2 mL) was irradiated for 20 min at 180 °C (Biotage Initiator apparatus). The medium was then concentrated *in vacuo* and 10 mL of CH_2Cl_2 were added. The organic layer was washed with a saturated solution of $NaHCO_3$, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by column chromatography (CH_2Cl_2–AcOEt (100 : 0 → 90 : 10)), providing 1,4-di(benzoyl)-piperazine-2,5-dione **5h** in 56% yield (0.318 g) as a white powder. Mp (decomposed) = 207 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.54 (s, 4H), 7.39–7.65 (m, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 48.8, 128.5, 128.9, 133.1, 133.8, 166.6, 170.9; HRMS (FAB+) m/z calcd for $C_{18}H_{14}N_2O_4$ [M + H$^+$] 323.1032, found 323.1042.

(3*R*)-1,4-Di(benzoyl)-3-*iso*propylpiperazine-2,5-dione 5j

Mp = 77 °C; $[\alpha]_D^{20} = -17.6$ ($c = 1.08$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.18 (t, 6H), 2.22–2.41 (m, 1H), 4.48 (d, 1H, J_{AB} = 18.8 Hz), 4.88 (d, 1H, J_{AB} = 18.8 Hz), 4.94 (d, 1H, $J = 8.4$ Hz), 7.40–7.71 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.5, 19.7, 32.6, 48.5, 64.2, 128.3 to 132.9, 134.1, 134.3, 167.0, 167.9, 171.1, 171.6; HRMS (FAB+) m/z calcd for $C_{21}H_{20}N_2O_4$ [M + H$^+$] 365.1501, found 365.1514.

1-(Benzoyl)-3-[(benzoyl)amino]-4-hydroxy-3-pyrrolin-2-one 6h

Typical procedure for the rearrangement. To a solution of 1,4-di(benzoyl)-piperazine-2,5-dione **5h** (0.077 g, 0.24 mmol) in dry THF (5 mL) was added *t*BuOK (0.030 g, 0.26 mmol) at r.t. The solution was stirred for 12 hours under an argon atmosphere. The medium was then diluted with AcOEt (10 mL), washed with a solution of 0.1 N HCl (20 mL), and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the desired compound was obtained (0.054 g, 69% yield) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.44 (s, 2H), 7.21–8.05 (m, 11H), 12.50 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 46.8, 104.2, 127.4 to 133.4, 131.0, 134.3, 156.5, 165.3, 167.2, 168.3; HRMS (FAB+) m/z calcd for $C_{18}H_{14}N_2O_4$ [M + H$^+$] 323.1032, found 323.1026.

(5*R*)-1-(Benzoyl)-3-[(benzoyl)amino]-4-hydroxy-5-*iso*propyl-3-pyrrolin-2-one 6j

Mp = 94 °C; $[\alpha]_D^{20} = -137.3$ ($c = 1.02$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.96 (d, 3H, $J = 7.0$ Hz), 1.16 (d, 3H, $J = 7.1$ Hz), 2.39–2.55 (m, 1H), 4.89 (d, 1H, $J = 2.8$ Hz), 7.29–8.02 (m, 11H), 12.57 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.6, 18.0, 29.3, 61.4, 103.9, 127.4 to 133.2, 131.0, 134.9, 160.1, 165.8, 167.2, 168.7; HRMS (FAB+) m/z calcd for $C_{21}H_{20}N_2O_4$ [M + H$^+$] 365.1501, found 365.1495.

1,4-Di(acetyl)-piperazine-2,5-dione 5k

A solution of piperazine-2,5-dione (0.424 g, 3.72 mmol) in acetic anhydride (2 mL) was irradiated for 26 min at 180 °C (Biotage Initiator apparatus). The medium was then concentrated *in vacuo* and purified by column chromatography (CH_2Cl_2–AcOEt (100 : 0 → 90 : 10)), providing 1,4-diacetyl-piperazine-2,5-dione in 76% yield (0.560 g) as white crystals. Mp = 97 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.52 (s, 6H), 4.55 (s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.7, 47.1, 166.0, 170.8; HRMS (FAB+) m/z calcd for $C_8H_{10}N_2O_4$ [M + H$^+$] 199.0719, found 199.0730.

1,2,4-Tri(acetyl)-piperazine-2,5-dione 7

To a solution of 1,4-di(acetyl)-piperazine-2,5-dione **5k** (0.070 g, 0.35 mmol) in dry THF (5 mL) was added tBuOK (0.044 g, 0.39 mmol) at r.t. The solution was stirred for 12 hours under an argon atmosphere. The medium was then diluted with AcOEt (10 mL), washed with a solution of 0.1 N HCl (20 mL), dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by column chromatography (CH_2Cl_2–AcOEt, 100 : 0 → 96 : 4). The desired compound was obtained (0.031 g, 37% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.41 (s, 3H), 2.52 (s, 3H), 2.55 (s, 3H), 3.82 (d, 1H, J_{AB} = 18.1 Hz), 4.95 (d, 1H, J_{AB} = 18.1 Hz), 6.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 26.6, 26.9, 27.4, 46.5, 68.5, 162.3, 165.0, 170.6, 171.2, 197.5; HRMS (FAB+) m/z calcd for $C_{10}H_{12}N_2O_5$ [M + H$^+$] 241.0824, found 241.0825.

(*Z*)-1-Acetyl-3-ethylene-piperazine-2,5-dione 8

To a solution of 1,2,4-tri(acetyl)-piperazine-2,5-dione **7** (0.162 g, 0.68 mmol) in 10 mL of dry THF was added LiAlH(O*t*Bu)$_3$ (1.01 mmol) at r.t. under stirring and an argon atmosphere. After 2 hours, AcOEt (30 mL) was added. The organic layer was washed with 0.1 N HCl, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was then purified by silica gel column chromatography (CH_2Cl_2–MeOH (100 : 0 → 96 : 4)). The desired compound was obtained (0.103 g, 83% yield) as a white powder.

Mp = 145 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.80 (d, 3H, J = 7.6 Hz), 2.54 (s, 3H), 4.37 (s, 2H), 6.34 (q, J = 7.6 Hz), 8.66 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 11.7, 27.1, 45.9, 119.4, 127.3, 159.7, 163.9, 172.6; HRMS (FAB+) m/z calcd for $C_8H_{10}N_2O_3$ [M + H$^+$] 183.0770, found 183.0775.

(5*R*)-4-Allyloxy-1-benzoyl-3-[(benzoyl)amino]-5-*iso*propyl-3-pyrrolin-2-one 11j

To a solution of (5*R*)-1-(benzoyl)-3-[(benzoyl)amino]-4-hydroxy-5-*iso*propyl-3-pyrrolin-2-one **6j** (0.152 g, 0.42 mmol) in dry DMSO (5 mL) was added KOH in powder form (0.021 g, 0.37 mmol) with stirring. Gentle warming was necessary for dissolution. The mixture changed color from pink to deep violet. Allyl bromide (0.03 mL, 0.38 mmol) was then added and the medium was allowed to stir under an argon atmosphere for 6 h. AcOEt (10 mL) was then added. The organic layer was washed with 0.1 N HCl (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by column chromatography (CH_2Cl_2–AcOEt, 100 : 0 → 80 : 20), providing the derivative **11j** (0.120 g) as a colorless oil in 71% yield. $[\alpha]_D^{20} = -160.4$ (c = 1.11, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.10 (d, 3H, J = 7.0 Hz), 1.23 (d, 3H, J = 7.1 Hz), 2.45–2.59 (m, 1H), 4.77–4.92 (m, 2H), 5.00 (d, 1H, J = 2.5 Hz), 5.24–5.39 (m, 2H), 5.85–6.02 (m, 1H), 7.33–7.82 (m, 11H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.3, 18.0, 29.7, 61.8, 71.5, 103.1, 119.1, 127.4 to 132.3, 132.7, 134.9, 168.1, 168.2, 168.3, 169.0; HRMS (FAB+) m/z calcd for $C_{24}H_{24}N_2O_4$ [M + H$^+$] 405.1814, found 405.1819.

(3*S*,5*R*)-3-Allyl-1-(benzoyl)-3-[(benzoyl)amino]-5-*iso*propylpyrrolidine-2,4-dione 12j

A solution of (5*R*)-4-allyloxy-1-benzoyl-3-[(benzoyl)amino]-5-*iso*propyl-3-pyrrolin-2-one **11j** (0.020 g, 0.05 mmol) in toluene (3 mL) with some drops of DMSO was irradiated for 30 min at 170 °C (Biotage Initiator apparatus). The medium was then concentrated *in vacuo* and the crude residue was purified by column chromatography (CH_2Cl_2–AcOEt, 100 : 0 → 95 : 5), providing **12j** in 74% yield (0.015 g) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.17 (d, 3H, J = 6.9 Hz), 1.19 (d, 3H, J = 6.6 Hz), 2.50–2.62 (m, 3H), 4.73 (d, 1H, J = 4.4 Hz), 5.20–5.36 (m, 2H), 5.64–5.81 (m, 1H), 6.51 (br s, 1H), 7.32–7.95 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.9, 19.4, 29.8, 38.2, 62.6, 67.3, 123.0, 127.4 to 133.9, 166.7, 170.2, 171.0, 205.1.

1-*tert*-Butoxycarbonylamino-8,9-dioxo-7-aza-bicyclo[4.2.1]non-3-ene-7-carboxylic acid *tert*-butyl ester 14a

To a stirred solution of 3,5-*trans*-diallyl-1-(*tert*-butoxycarbonyl)-3-[(*tert*-butoxycarbonyl)amino]pyrrolidine-2,4-dione **13a** (0.226 g, 0.57 mmol) in dichloromethane (8 mL) was added Grubbs' catalyst (2% mol of benzylidene-[1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]-dichloro (tricyclohexyl phosphane) ruthenium, 0.010 g in 2 mL of dichloromethane, 0.0115 mmol). The reaction mixture was stirred for 2 h. DMSO (0.04 mL, 0.48 mmol, 50 equiv. related to catalyst) was then added and the solution was stirred for an additional 12 hours. After concentration *in vacuo*, the residue was purified by flash chromatography on silica gel (CH_2Cl_2–AcOEt, 100 : 0 → 85 : 15) to give the compound **14a** (0.176 g, 84% yield) as a solid. Mp = 104 °C; t_r = 10.937 min; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.35 (s, 9H), 1.54 (s, 9H), 2.22–2.33 (m, 1H), 2.55–2.68 (m, 1H), 2.36–2.48 (m, 1H), 2.80–2.92 (m, 1H), 4.70 (m, 1H), 5.40 (s, 1H), 5.46–5.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 28.0, 28.2, 30.3, 33.7, 62.0, 64.4, 81.6, 84.2, 121.9, 124.5, 148.4, 154.6, 170.3, 204.7. HRMS (FAB+) m/z calcd for $C_{18}H_{26}N_2O_6$ [M + H$^+$] 367.4092, found 367.4101.

(5*R*)-4-Allyloxy-3-[allyl-(*tert*-butoxycarbonyl)amino]-1-(*tert*-butoxycarbonyl)-5-*iso*propyl-3-pyrrolin-2-one 17

To a stirred solution of (5*R*)-1-(*tert*-butoxycarbonyl)-3-[(*tert*-butoxycarbonyl)amino]-4-hydroxy-5-*iso*propyl-3-pyrrolin-2-one **6e** (0.713 g, 2.00 mmol) in dry DMSO (8 mL) was added KOH powder (0.280 g, 5.01 mmol). Gentle warming was necessary for total dissolution. The mixture turned from pink to deep violet. Allyl bromide (0.44 mL, 5.01 mmol) was then added and the medium was stirred under an argon atmosphere for 12 hours. The reaction mixture was diluted with AcOEt (16 mL) and then washed with 0.1 N HCl (16 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (CH_2Cl_2–AcOEt, 100 : 0 → 80 : 20), providing the derivative **17** (0.665 g) as a colorless oil in 76% yield. $[\alpha]_D^{20} = -46.0$ (c = 2.20, CH_2Cl_2); t_r = 14.549 min; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.79 (d, 3H, J = 6.9 Hz), 1.10 (d, 3H, J = 7.2 Hz), 1.41 (s, 9H), 1.53 (s, 9H), 2.38–2.50 (m, 1H), 3.79–4.34 (m, 2H), 4.28 (s, 1H), 4.68–4.87 (m, 2H), 5.10–5.40 (m, 4H), 5.81–6.00 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 16.4, 18.9, 28.2, 28.4, 29.5, 52.1, 62.2, 71.5, 81.1, 82.8, 109.3, 119.0, 131.7, 133.2, 149.3, 154.9, 166.9, 167.9; HRMS (FAB+) m/z calcd for $C_{23}H_{36}N_2O_6$ [M + H$^+$] 437.2652, found 437.2627.

(3*S*,5*R*)-3-Allyl-3-[allyl-(*tert*-butoxycarbonyl)amino]-1-(*tert*-butoxycarbonyl)-5-*iso*propylpyrrolidine-2,4-dione 18

A solution of (5*R*)-4-allyloxy-3-[allyl-(*tert*-butoxycarbonyl)-amino]-1-(*tert*-butoxycarbonyl)-5-*iso*propyl-3-pyrrolin-2-one **17** (0.180 g, 0.45 mmol) in toluene (3 mL) containing some drops of DMSO, was irradiated for 30 min at 170 °C (Biotage Initiator apparatus). The medium was then concentrated *in vacuo* and the crude residue was purified by column chromatography on silica gel (CH_2Cl_2–AcOEt, 100 : 0 → 95 : 5), providing compound **18** as a colorless oil (0.143 g, 73% yield). $[\alpha]_D^{20} = -98.0$ (c = 1.48, CH_2Cl_2); t_r = 15.413 min; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.06 (d, 3H, J = 7.1 Hz), 1.18 (d, 3H, J = 6.9 Hz), 1.40 (s, 9H), 1.55 (s, 9H), 2.39–2.52 (m, 1H), 2.39–2.67 (m, 2H), 3.93 (d, 1H, J = 5.9 Hz), 4.01 (br s, 2H), 5.10–5.23 (m, 2H), 5.10–5.40 (m, 2H), 5.48–5.62 (m, 1H), 5.81–5.98 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.6, 21.4, 28.0, 28.1, 31.4, 37.4, 46.3, 68.4, 69.4, 81.8, 83.4, 115.8, 122.1, 128.4, 135.6, 150.0, 155.3, 171.8, 206.8; HRMS (FAB+) m/z calcd for $C_{23}H_{36}N_2O_6$ [M + H$^+$] 437.2652, found 437.2649.

Baikiain spiro-derivative 15a

To a stirred solution of (3*S*,5*R*)-3-allyl-3-[allyl-(*tert*-butoxycarbonyl)amino]-1-(*tert*-butoxycarbonyl)-5-*iso*propylpyrrolidine-2,4-dione **18** (0.105 g, 0.24 mmol) in dichloromethane (5 mL) was added Grubbs' catalyst (2% mol of benzylidene-[1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]-dichloro (tricyclohexyl phosphane) ruthenium, 0.004 g, in 2 mL of dichloromethane, 0.0048 mmol). The reaction mixture was stirred for 2 hours.

DMSO (0.02 mL, 0.24 mmol, 50 equiv. related to catalyst) was then added and the solution was stirred for an additional 12 hours. After concentration *in vacuo*, the residue was purified by flash chromatography on silica gel (CH_2Cl_2–AcOEt, 100 : 0 → 98 : 2) to produce the compound **15a** (0.086 g, 88% yield) as a solid. Mp = 124 °C; t_r = 14.275 min; $[\alpha]_D^{20} = -89.0$ (c = 1.90, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.04 (d, 3H, J = 7.0 Hz), 1.08 (d, 3H, J = 7.2 Hz), 1.35 (s, 9H), 1.50 (s, 9H), 2.24–2.36 (m, 1H), 2.40–2.52 (m, 2H), 3.98–4.02 (m, 2H), 4.23 (d, 1H, J = 4.5 Hz), 5.60–5.70 (m, 1H), 5.86–5.94 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.1, 19.2, 28.0, 28.2, 30.6, 30.9, 43.6, 62.8, 67.0, 81.7, 83.8, 118.5, 126.0, 150.0, 155.1, 171.1, 206.2; HRMS (FAB+) m/z calcd for $C_{21}H_{32}N_2O_6$ [M + H$^+$] 409.2339, found 409.2347.

(3*R*)-3-*iso*Propyl-1-oxo-1,3,5,8-tetrahydro-4-oxa-2,9-diaza-cyclopentacyclooctene-2,9-dicarboxylic acid di-*tert*-butyl ester 16a

To a stirred solution of (5*R*)-4-allyloxy-3-[allyl-(*tert*-butoxycarbonyl)amino]-1-(*tert*-butoxycarbonyl)-5-*iso*propyl-3-pyrrolin-2-one **17** (0.403 g, 0.92 mmol) in dichloromethane (20 mL) was added Grubbs' catalyst (2% mol of benzylidene-[1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]-dichloro (tricyclohexyl phosphane) ruthenium, 0.016 g, in 2 mL of dichloromethane, 0.0185 mmol). The reaction mixture was stirred for 2 h. DMSO (0.08 mL, 0.92 mmol, 50 equiv. related to catalyst) was then added and the solution was stirred for an additional 12 hours. After concentration *in vacuo*, the residue was purified by flash chromatography on silica gel (CH_2Cl_2–AcOEt, 100 : 0 → 80 : 20) to produce the compound **16a** (0.295 g, 78% yield) as a colorless oil. The ^{1}H NMR spectrum of compound **16a** gave two sets of peaks for the methyl protons of one Boc and also two sets of peaks for the *iso*propyl group. A high-temperature ^{1}H NMR study in DMSO-d_6 allowed us to correlate this observation with E/Z isomerisation of the *N*1-Boc. Coalescence of the proton resonances occurred at 120 °C. Once back at room temperature, the splitting of the signals returned and the NMR spectrum was identical to the initial spectrum, allowing us to prove that the compound was not damaged. $[\alpha]_D^{20} = -66.9$ (c = 1.45, CH_2Cl_2); t_r = 13.428 min; ^{1}H NMR (DMSO-d_6, 400 MHz) at 25 °C: δ 0.60 (m, 1H), 0.72 (d, 2H, J = 7.0 Hz), 0.90 (m, 1H), 0.97 (d, 2H, J = 7.2 Hz), 1.28 (s, 3H), 1.34 (s, 6H), 1.53 (s, 9H), 2.18–2.37 (m, 1H), 3.39–3.61 (m, 1H), 4.17 (d, 1H, J = 2.5 Hz), 4.42–5.15 (m, 3H), 5.72–5.92 (m, 2H);^{13}C NMR ($CDCl_3$, 100 MHz) at 25 °C: δ 16.0, 18.5, 18.8, 28.1, 28.3, 29.8, 30.2, 49.7, 62.2, 63.6, 81.2, 81.5, 82.6, 109.0, 121.2, 136.5, 149.3, 154.6, 166.3, 167.3; HRMS (FAB+) m/z calcd for $C_{21}H_{32}N_2O_6$ [M + H$^+$] 409.2339, found 409.2324.

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