Pergamon

Tetrahedron 57 (2001) 5393–5401

TETRAHEDRON

N-Boc-2-acyl oxazolidine methodology combined with ring-closing metathesis: a new approach towards the enantioselective synthesis of α-(1-hydroxyalkyl) nitrogen heterocycles

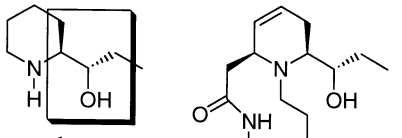
Claude Agami, François Couty* and Nicolas Rabasso

Laboratoire de Synthèse Asymétrique (UMR CNRS 7611), Université Pierre et Marie Curie, 4 place Jussieu, 75005 Paris, France

Received 9 February 2001; accepted 26 April 2001

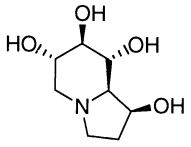
Abstract—A synthetic methodology, based on *N*-Boc-2-acyloxazolidine chemistry combined with ring-closing metathesis, allows the preparation of enantiopure piperidinic heterocycles showing a 2-(1-hydroxyalkyl) side-chain, a pattern commonly found in natural alkaloids. Synthesis of Δ-3,4-2,6-disubstituted piperidinic rings can thus be achieved with a good 2,6-*cis* or -*trans* stereocontrol, unless the substituent located at C_2 is not a phenyl group. Diastereoselective functionnalization of the Δ-3,4 alkene moiety and access to seven or eight-membered nitrogen rings are also key features of this methodology. © 2001 Elsevier Science Ltd. All rights reserved.

Nitrogen heterocycles α-substituted by a (1-hydroxyalkyl) side-chain constitute a framework frequently encountered in natural alkaloids.[1] This is the case in (−)-β-conhydrine **1**, a piperidinic alkaloid isolated from the seeds of the toxic *Conium maculatum* L.,[2] or in palustrine **2**[3], the toxic principle of *Equisetum paluster* L. This pattern is also found in indolizidinic alkaloids, such as (−)-castanospermine **3**, or (−)-slaframine **4**; due to their potent glycosidase inhibitory activity[4] they are intensively studied, among other aza-sugars, by the synthetic community. The improvement of the biological activity and selectivity of this class of compounds still calls for new synthetic strategies.

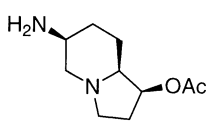


1

2



3



4

This paper reports a new approach[5] for the enantioselective synthesis of nitrogen heterocycles possessing the general structure depicted in Figure 1.

This methodology is based on the combination of the chemistry of *N*-Boc-2-acyl oxazolidines developed in our group,[6] and ring-closing metathesis.[7] The scope of this method includes: (i) an efficient *syn* stereocontrol of the C_6–C_7 amino alcohol moiety, (ii) the possibility of further diastereoselective functionalization of the C_3–C_4 alkene, (iii) a *cis* or *trans* (when n=1) stereocontrol of the C_2 and C_6 disubstituted piperidine, and (iv) an access (when R′=H) to larger unsaturated nitrogen rings.

The retrosynthetic scheme of our method is depicted in Scheme 1 for n=1. Unsaturated piperidinol **A** is accessible through alkaline hydrolysis of bicyclic oxazolidinone **B**, itself prepared by ring-closing metathesis of diolefinic compound **C**. The latter arises from alcohol **D** through an oxidation/Wittig olefination sequence. A *trans* C_6–C_7 stereocontrol results in **D** from the allylation of bicyclic oxazolidinone **E** through precedented acyl iminium chemistry.[8] Finally, oxazolidinone **E** derives via a trans-carbamation of *N*-Boc-α-hydroxy oxazolidine **F**, easily

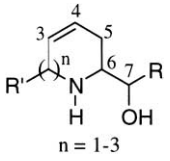
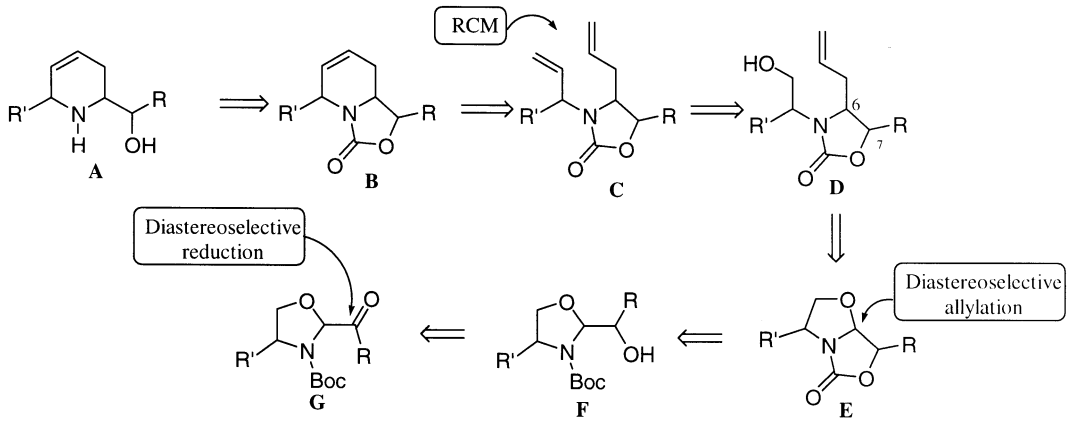


Figure 1.

Keywords: heterocycles; alkaloids; stereoselective.

* Corresponding author. Tel.: +33-1-44-273013; fax: +33-1-44-272620; e-mail: couty@ccr.jussieu.fr

PII: S0040-4020(01)00458-6



Scheme 1.

obtained by diastereoselective reduction of the starting *N*-Boc-2-acyl oxazolidine **G**.

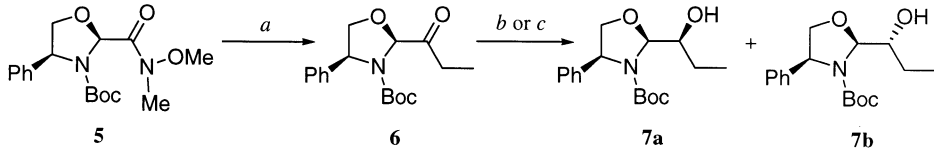
In order to test the viability of the above synthetic scheme, this study was initiated with our previously described phenyl glycinol-derived Weinreb amide **5** (R′=Ph), and although a wide range of acyl oxazolidines can be prepared starting from **5**, we choose to introduce an ethyl group (R=Et), aiming to synthetize (−)-β-conhydrine **1**.

1. Synthesis of α-(1-hydroxyalkyl) substituted nitrogen heterocycles

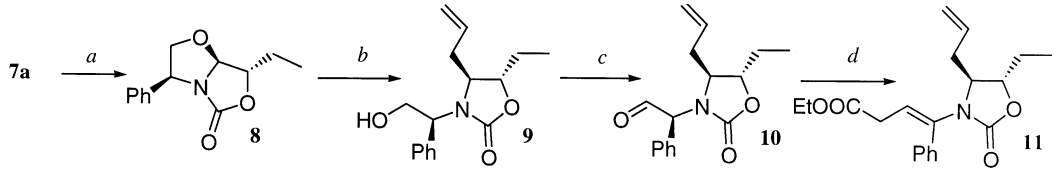
As shown in Scheme 2, reaction of ethylmagnesium bromide with **5** gave ketone **6** in good yield. $NaBH_4$-mediated reduction of **6** then gave diateroisomeric α-hydroxy oxazolidines **7a** and **7b** in a 86/14 ratio. Major stereoisomer **7a** was conveniently isolated pure after flash chromatography. When this reduction was conducted in the presence of cerium trichloride, the ratio of **7a** and **7b** was reversed (20/80), and major isomer **7b** was now isolated. The observed diastereoselectivity is in agreement with previous results[6] and is explained on the basis of a Felkin–Ahn control ($NaBH_4$ alone), or a chelated model ($NaBH_4$ in the presence of Ce^{III}).

Treatment of **7a** with NaH in THF gave oxazolidinone **8**, that was reacted with allyltrimethylsilane, in the presence of titanium tetrachloride, in order to afford **9** with high stereoselectivity. Transformation of this alcohol into the diolefinic substrate required for the ring-closing step (transfomation **D** → **C** in Scheme 1), requires its prior oxidation into **10**. Among the various conditions tested for this oxidation, only Dess–Martin periodinane gave a satisfactory result, affording unstable aldehyde **10** in good yield. However, Wittig olefination of this aldehyde failed to produce the required alkene, presumably because of an undesired enolisation. The less basic carboethoxy triphenyl phosphorane[9] led to unsaturated ester **11** in a reasonable yield, but with an isomerized alkene moiety, conjugated with the phenyl ring. This emphasizes the ease of enolization of the benzylic position in this substrate (Scheme 3).

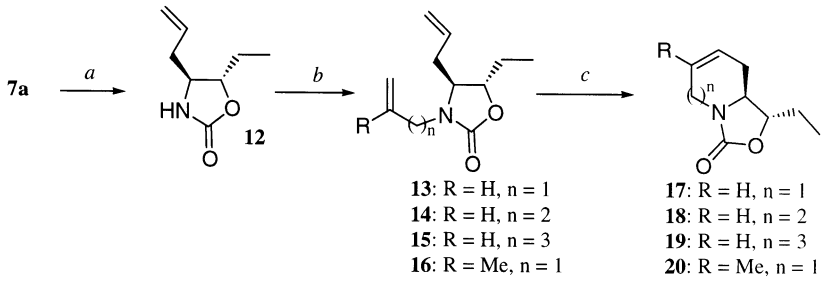
On the other hand, treatment of isomeric alcohol **7b** with NaH did not lead to any transcarbamation product, and this was ascribed[5] to a steric crowding between the ethyl group and the C_4 phenyl ring substituent. In order to synthetise diolefinic substrates required to test the RCM step, oxazolidinone **9** was reductively debenzylated to give **12**, and transformed into diolefinic oxazolidinones **13–16** by treatment with NaH and alkylation with the appropriate halogenoalkene. Ring-closing metathesis of these



Scheme 2. *Reagents and conditions*: *a* Ethylmagnesium bromide, Et_2O, rt. *b* $NaBH_4$, EtOH, −78°C, 71% overall for **7a**. *c* $NaBH_4$, EtOH, $CeCl_3$ ($7H_2O$), −78°C, 69% overall for **7b**.



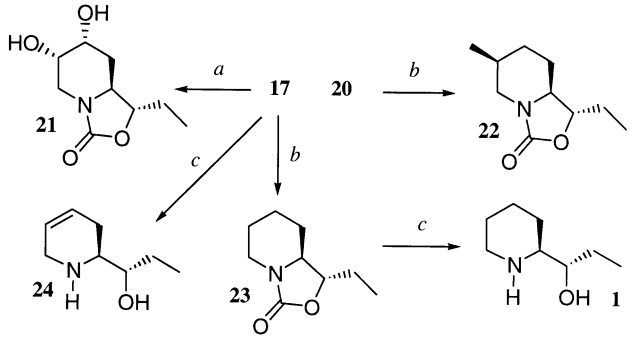
Scheme 3. *Reagents and conditions*: *a* NaH, THF, reflux, 98%. *b* allyltrimethylsilane, $TiCl_4$, −78°C, CH_2Cl_2, 71%. *c* Dess–Martin periodinane, CH_2Cl_2. *d* $(C_6H_5)_3P{=}CHCO_2Et$, benzene, 40% overall from **9**.



Scheme 4. *Reagents and conditions*: *a* Na (3.5 equiv.), EtOH, THF, NH_3, 93%. *b* NaH, DMF, C_3H_7Br, 74%; **13**: C_4H_9Br, 42%; **14**:, $C_5H_{10}Br$, 72%, **15**; C_4H_7Cl, 54%, **16**. *c* Grubbs' catalyst (2.5 molar ratio), CH_2Cl_2, reflux, **17**: 79%, **18**: 80%, **19**: 86%, **20**: 74%.

compounds then occured in the presence of Grubbs' catalyst (2.5% molar ratio), and yielded bicyclic oxazolidinones **17**–**20** (Scheme 4).

Reactivity of the above bicyclic oxazolidinones was next studied. AM1 calculations performed on compound **17** shows a significant steric crowding of the *endo* diastereoface of the alkene moiety in this bicyclic compound.[5] Indeed, dihydroxylation of **17** gave *exo* diol **21** as a unique stereoisomer, and the relative configuration of the newly created stereocenters was secured by X-ray radiocrystallography. On the other hand, hydrogenation of compound **20** afforded **22** with a 72% de, and the structure of the major isomer was assigned on the basis of the previous result (i.e. *exo* hydrogenation). Finally, hydrogenation of **17**, followed by alkaline hydrolysis gave (−)-β-conhydrine **1**, whereas hydrolysis of **17** afforded the unsaturated analog **24** (Scheme 5).



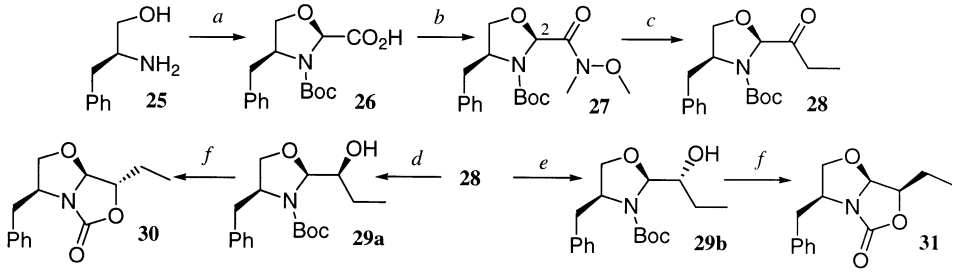
Scheme 5. *Reagents and conditions*: *a* OsO_4, NMO, acetone/water, 45%. *b* Pd/C, EtOH, 92% (**24**), 88% (**22**). *c* LiOH, EtOH, THF, reflux, 45% (**1**), 54% (**24**).

Still remains unsolved the formation of a stereogenic center at C_2 (R′ other than H, in Fig. 1). In order to circumvent the failure of the Wittig olefination of **10** (R′=Ph), possessing a relatively acidic hydrogen in α position both to a carbonyl and phenyl groups, we decided to start with another β-amino alcohol.

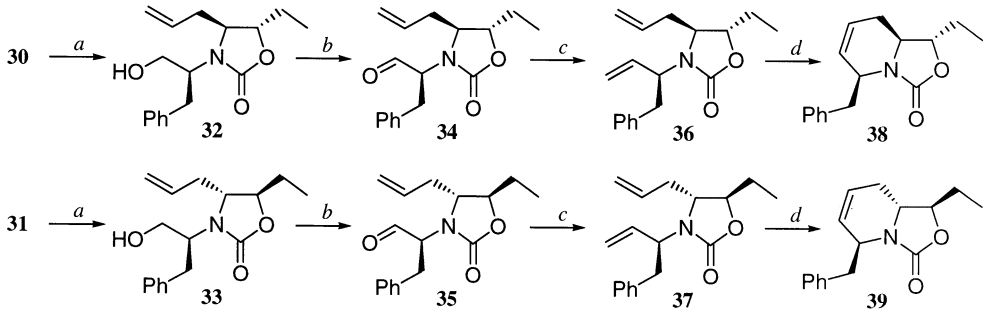
2. Synthesis of α,α′-disubstituted-α-(1-hydroxyalkyl) nitrogen heterocycles

(*S*)-Phenylalaninol-derived Weinreb amide **27** was prepared following our reported procedure. No loss of selectivity was observed for the C_2 stereocontrol, compared to **5**. Ketone **28** was then stereoselectively reduced to give **29a** (de: 76%), or **29b** (de: 58%). In these steps, similar selectivities were observed, compared to the phenyl-substituted substrate. However, an important difference of reactivity appeared during the next step, i.e. the transcarbamation. Indeed, in this case, both stereoisomers **29a** and **29b** could be conveniently cyclized to give the corresponding bicyclic oxazolidinones **30** and **31** whereas substrate **7b** was unreactive under similar conditions. As a matter of fact, the larger conformational mobility of the benzyl group compared to the phenyl group in **7b**, induces less steric crowding in the course of the cyclization of **29b** (Scheme 6).

Allylation of compounds **30** and **31** stereoselectively gave *trans* adducts **32** and **33**. Since it was previously demonstrated[9] that this reaction proceeds through an intermediate acyliminium ion, these results show that the stereocenter bearing the benzylic substituent on the oxazolidine ring has a negligible stereodirecting effect in this allylation, compared to the α-ethyl substituent. Oxidation of **32** and **33** afforded aldehydes **34** and **35** which were now olefinated without problems to give **36** and **37**. The overall yield of this



Scheme 6. *Reagents and conditions*: *a* (i) Ethyl glyoxylate, (ii) $(Boc)_2O$, (iii) LiOH, 77% overall. *b* Isobutyl chloroformiate, NHMe(OMe), HCl, 79%. *c* Ethylmagnesium bromide, Et_2O, rt, 72%. *d* $NaBH_4$, EtOH, −78°C, 72%. *e* $NaBH_4$, $CeCl_3$, EtOH, −78°C, 54%. *f* NaH, THF, reflux, 71% (**30**), 68% (**31**).



Scheme 7. *Reagents and conditions*: *a* allyltrimethylsilane, $TiCl_4$, −78°C, CH_2Cl_2, 77% (**32**), 65% (**33**). *b* Dess–Martin periodinane, CH_2Cl_2. *c* Ph_3PCH_3Br, *n*BuLi, THF, −20°C, 80% overall (**36**), 40% overall (**37**). *d* Grubbs' catalyst (2.5 molar ratio), CH_2Cl_2, reflux, 83% (**38**), 74% (**39**).

sequence was nevertheless lower in case of substrate **32**. Finally, ring-closing metathesis of these diolefinic substrates yielded *cis* and *trans* disubstituted piperidinic compounds **38** and **39** (Scheme 7).

In conclusion, the above reported procedure allows a general access to enantiopure stereodefined nitrogen heterocycles. Application to the synthesis of bioactive alkaloids showing more complex squeletton is currently under study in our group.

3. Experimental

3.1. General comments

^1H- and ^{13}C spectra ($CDCl_3$ solution unless otherwise stated) were recorded on a Bruker ARX 250 spectrometer at 250 and 62.9 MHz, respectively; chemical shifts are reported in ppm from TMS. Optical rotations were determined with a Perkin–Elmer 141 instrument. GC analysis were run on a Hewlett–Packard 5890 instrument using a capillary column (OV 17) of 30 m. Mass spectra were recorded on a GC/MS Varian Saturn 2000. Elemental analysis were performed by the 'Sevice Regional de Microanalyses de l'Université P. et M. Curie'. All reactions were carried out under argon. Column chromatography were performed on silica gel 230–400 mesh by using various mixtures of diethyl ether (E), ethyl acetate (AcOEt) and petroleum ether (PE). TLC were run on Merck Kieselgel $60F_{254}$ plates. Melting points are uncorrected. THF and ether were distilled from sodium/benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Mention of 'usual workup' means: (i) decantation of the organic layer, (ii) extraction of the aqueous layer with ether, (iii) drying of the combined organic phases over $MgSO_4$, (iv) solvent evaporation under reduced pressure. Composition of stereoisomeric mixtures was determined by NMR analysis on crude products before any purification.

3.1.1. (2*S*,4*S*)-3-*tert*-Butoxycarbonyl-2-(propionyl)-4-phenyl-1,3-oxazolidine 6. To a solution of Weinreb amide **5** (13.5 g, 40 mmol) in ether (130 mL), cooled to 5°C, was added dropwise a solution of ethylmagnesium bromide (3N solution in ether, 20 mL, 60 mmol). At the end of the addition, the suspension was stirred for 0.5 h and hydrolyzed by addition of a saturated aqueous solution of NH_4Cl (50 mL). Addition of water (100 mL) was followed by usual workup to give crude **6** as an oil (11 g) that was used without further purifications for the next step. An analytical sample was purified by flash chromatography (E/PE: 2/8). R_f: 0.53 (E/PE: 4/6); $[\alpha]_D^{20}=-21.5$ (*c* 0.5, $CHCl_3$); IR (film): 1812, 1708 cm^{-1}; ^1H NMR: 1.06 (t, *J*=7.5 Hz, 3H), 1.21 (bs, 9H), 2.58–2.65 (m, 2H), 3.93 (t, *J*=8.5 Hz, 1H), 4.34 (t, *J*=8.5 Hz, 1H), 4.80 (bs, 1H), 5.13 (bs, 1H), 7.17–7.38 (m, 5H); ^{13}C NMR: 7.3, 28.2 (CH_3), 30.1 (CH_2), 59.2 (CH), 69.6 (CH_2), 84.3 (Cq), 89.8, 126.9, 127.1, 128.6, (CH), 140.9, 154.8 (Cq); Anal. calcd for $C_{17}H_{23}NO_4$: C: 66.86; H: 7.59; N: 4.59. Found: C: 66.69; H: 7.88; N: 4.50.

3.1.2. [2*S*,2(1*S*),4*S*]-3-*tert*-Butoxycarbonyl-2-(1-hydroxy-propyl)-4-phenyl-1,3-oxazolidine 7a and [2*S*,2(1*R*),4*S*]-3-*tert*-butoxycarbonyl-2-(1-hydroxy-propyl)-4-phenyl-1,3-oxazolidine 7b. To a solution of crude acyl oxazolidine **6** (11 g, 36 mmol), in ethanol (240 mL), cooled to −78°C, was added in one portion sodium borohydride (2.7 g, 72 mmol). The mixture was stirred for 0.5 h at −78°C and hydrolyzed by addtion of a saturated aqueous solution of NH_4Cl (50 mL). After warming to rt, the ethanol was distilled off under reduced pressure. Addition of water and ether to the residue was followed by usual workup. Crude hydroxy oxazolidine (de: 72%) was purified by flash chromatography (E/PE: 2/8) to give pure title compound **7a** as an oil (7.86 g, 71% overall yield from **5**). R_f: 0.54 (E/PE: 4/6); $[\alpha]_D^{20}=+3.7$ (*c* 0.7, $CHCl_3$); IR (film): 3441, 3030, 1709 cm^{-1} ^1H NMR: 0.98 (t, *J*=7.5 Hz, 3H), 1.22 (bs, 9H), 1.36–1.55 (m, 1H), 1.63–1.79 (m, 1H), 3.61–3.70 (m, 1H), 3.88 (dd, *J*=8.5 and 6.8 Hz, 1H), 4.22 (dd, *J*=6.8 and 8.6 Hz, 1H), 4.85 (t, *J*=6.8 Hz, 1H), 5.04 (d, *J*=7.7 Hz 1H), 7.19–7.28 (m, 5H); ^{13}C NMR: 9.3 (CH_3), 26.4 (CH_2), 28.1 (CH_3), 61.0 (CH), 73.6 (CH_2), 75.1 (CH) 81.9 (Cq), 92.6, 126.4, 127.7, 128.6, (CH), 140.3, 154.5 (Cq); Anal. Calcd for $C_{17}H_{25}NO_4$: C: 66.43; H: 8.20; N: 4.56. Found: C: 66.68; H: 8.09; N: 4.29. When the same reaction was conducted in the presence of $CeCl_3$ ($7H_2O$) (1.5 equiv.), added prior to the addition of sodium borohydride, crude hydroxy oxazolidine **7b** (de 60%) was now obtained. Pure **7b** was isolated as above (69%). R_f: 0.36 (E/PE: 4/6); oil; $[\alpha]_D^{20}=+30.5$ (*c* 0.8, $CHCl_3$); ^1H NMR: 1.05 (t, *J*=7.5 Hz, 3H), 1.37 (bs, 9H), 1.55–1.70 (m, 2H), 3.82–3.92 (m, 1H), 4.10 (dd, *J*=8.9 and 5.5 Hz, 1H), 4.32 (dd, *J*=7.4 and 8.9 Hz, 1H), 4.88–5.02 (m, 1H), 5.13 (d, *J*=3.7 Hz 1H), 7.25–7.39 (m, 5H); ^{13}C NMR: 10.9 (CH_3), 26.0 (CH_2), 28.6 (CH_3), 61.0 (CH), 73.3 (CH_2 and CH), 81.9 (Cq), 92.9, 126.9, 127.9, 128.9, (CH), 140.9, 154.9 (Cq).

3.1.3. (3*S*,6*S*,7*S*)-6-Ethyl-3-phenyltetrahydro-1,5-dioxa-3a-aza-pentalen-4-one 8. To a solution of alcohol **7a** (3.2 g, 10.4 mmol) in THF (150 mL) was added sodium hydride (60% wt, 833 mg, 20.8 mmol). When hydrogen evolution had ceased, the mixture was refluxed for 2 h and hydrolyzed by addition of a saturated aqueous solution of NH_4Cl (50 mL). Usual workup gave a pale yellow solid that was washed with small portions of petroleum ether. Compound **8** was obtained as a white solid (2 g, 82%); R_f: 0.42 (E/PE: 8/2); mp: 106–108°C; $[\alpha]_D^{20}=-83.6$ (*c* 0.6, $CHCl_3$); ^1H NMR: 1.10 (t, *J*=7.5 Hz, 3H), 1.84–1.87 (m, 2H), 4.29–4.33 (m, 2H), 4.51 (td, *J*=3.0 and 6.5 Hz, 1H), 4.70 (dd, *J*=3.4 and 6.5 Hz, 1H), 5.03 (d, *J*=2.5 Hz, 1H), 7.37–7.40 (m, 5H); ^{13}C NMR: 8.7 (CH_3), 26.4 (CH_2), 61.1 (CH), 75.8 (CH_2), 80.6, 94.9, 127.9, 128.6, 128.7 (CH), 136.8 (Cq); Anal. calcd for $C_{13}H_{15}NO_3$: C: 66.94; H: 6.48; N: 6.00. Found: C: 64.82; H: 6.58; N: 5.51.

3.1.4. (4*S*,5*S*,6*S*)-4-Allyl-5-ethyl-3-(2-hydroxy-1-phenyl-ethyl)-oxazolidin-2-one 9. To a solution of **8** (2.36 g, 10 mmol) in dichloromethane (50 mL) was added allyltrimethylsilane (6.4 mL, 40.5 mmol). The solution was cooled to −78°C and a solution of $TiCl_4$ (1 M solution in dichloromethane, 20 mL, 20 mmol) was added dropwise. The solution was warmed to rt and hydrolyzed with a saturated aqueous solution of $NaHCO_3$. Usual workup (dichloromethane) gave a pale yellow solid that was washed with small portions of petroleum ether. Compound **9** was obtained as a white solid (1.94 g, 71%); R_f: 0.62 (E); mp: 74–76°C; $[\alpha]_D^{20}=+1.5$ (*c* 0.6, $CHCl_3$); ^1H NMR: 0.80 (t, *J*=7.5 Hz, 3H), 1.41–1.53 (m, 2H), 2.17–2.22 (m, 2H), 3.08–3.15 (m, 1H), 3.81 (dd, *J*=3.3 Hz, 1H), 4.00–4.07 (m, 1H), 4.24–4.29 (m, 1H), 4.35–4.39 (m, 1H), 4.66 (s, 1H), 5.02–5.10 (m, 2H), 5.47–5.54 (m, 1H), 7.16–7.29 (m, 5H); ^{13}C NMR: 9.2 (CH_3), 28.2, 36.3 (CH_2), 59.8, 61.6 (CH), 64.1 (CH_2), 79.9 (CH), 120.5 (CH_2), 127.6, 128.7, 129.3, 131.5 (CH), 136.7, 157.8 (Cq); IR (Nujol): 3378, 1704 cm^{-1}; Anal. calcd for $C_{16}H_{21}NO_3$: C: 69.79; H: 7.69; N: 5.09. Found: C: 69.71; H: 7.54; N: 5.03.

3.1.5. (2*S*,4*S*,5*S*)-(4-Allyl-5-ethyl-2-oxo-oxazolidin-3-yl)-phenyl-acetaldehyde 10. To a solution of **9** (158 mg, 0.57 mmol) in dichloromethane (5 mL) was added Dess–Martin Periodinane (485 mg, 1.14 mmol). The suspension was stirred at rt for 2 h, and then diluted with ether (25 mL) and petroleum ether (50 mL). Filtration over a pad of Celite and concentration gave crude aldehyde **10** as an oil (180 mg) that was used without further purifications. R_f: 0.77 (AcOEt/PE: 1/1); IR (film): 1730 cm^{-1}; ^1H NMR: 0.89 (t, *J*=7.5 Hz, 3H), 1.53–1.74 (m, 2H), 1.77–1.99 (m, 2H), 3.06 (s, 1H), 3.39 (q, *J*=5.0 Hz, 1H), 4.12 (q, *J*=5.0 Hz, 1H), 4.90–5.17 (m, 2H), 5.37–5.65 (m, 1H), 7.20–7.39 (m, 5H), 9.74 (s, 1H); ^{13}C NMR: 8.9 (CH_3), 27.8, 36.8 (CH_2), 58.4, 66.2, 80.9 (CH), 120.1 (CH_2), 128.9, 129.3, 129.5, 131.8 (CH), 136.3, 158.3 (Cq), 195.1 (CH).

3.1.6. (4*S*,5*S*)-4-(4-Allyl-5-ethyl-2-oxo-oxazolidin-3-yl)-4-phenyl-but-3-enoic acid ethyl ester 11. To a solution of the above crude aldehyde **10** (180 mg) in benzene (7 mL) was added carboethoxytriphenyl phosphorane (344 mg, 1 mmol). After 1 h, usual workup gave an oil that was purified by flash chromatography (AcOEt/PE: 15/85). Title compound was obtained as a clear oil (78 mg, 40% overall yield from **9**): R_f: 0.78 (AcOEt/PE: 3/7); $[\alpha]_D^{20}=-41.3$ (*c* 1.4, $CHCl_3$); IR (film): 2977, 2934, 1744 cm^{-1}; ^1H NMR: 0.95 (t, *J*=7.5 Hz, 3H), 1.21 (t, *J*=7.5 Hz, 3H), 1.52–1.73 (m, 2H), 1.99–2.25 (m, 2H), 3.15 (dd, *J*=8.5 and 19.0 Hz, 1H), 3.30 (dd, *J*=5.2 and 19.0 Hz, 1H), 3.40–3.45 (m, 1H), 4.05–4.18 (m, 3H), 4.95–5.05 (m, 2H), 5.40–5.47 (m, 1H), 6.07 (dd, *J*=5.3 and 8.5 Hz, 1H), 7.21–7.33 (m, 5H); ^{13}C NMR: 9.5, 14.6 (CH_3), 28.4, 34.3, 37.9 (CH_2), 59.7 (CH), 61.2 (CH_2), 80.6 (CH), 120.1 (CH_2), 123.3, 127.4, 129.2, 131.8 (CH), 135.2, 135.7, 155.5, 171.5 (Cq).

3.1.7. (4*S*,5*S*)-4-Allyl-5-ethyl-oxazolidin-2-one 12. To a solution of **7a** (926 mg, 3.36 mmol) in THF (5 mL), EtOH (2 mL) and ammonia (40 mL), cooled at −40°C was added sodium portionwise (271 mg, 11.8 mmol). After 20 min, the mixture was quenched by addition of solid ammonium chloride (2 g), and stirred at rt for 1 h. The residue was taken up in water, and usual workup (dichloromethane) gave an oil that was purified by flash chromatography (E/PE: 1/1). Title oxazolidinone was obtained as an oil (486 mg, 93%). R_f: 0.40 (E); GC (70–220°C, rate of 10°C/min): tr=8.46 min; $[\alpha]_D^{20}=-59.7$ (*c* 2.4, $CHCl_3$); IR (film): 3220, 3019, 1747 cm^{-1}; ^1H NMR: 0.94 (t, *J*=7.5 Hz, 3H), 1.58–1.70 (m, 2H), 2.20–2.27 (m, 2H), 3.36–3.49 (m, 1H), 3.99–4.12 (m, 1H), 5.05–5.13 (m, 2H), 5.59–5.74 (m, 1H), 6.65 (bs, 1H); ^{13}C NMR: 9.4 (CH_3), 28.0, 38.1 (CH_2), 57.2, 83.5 (CH), 119.7 (CH_2), 132.6 (CH), 160.0 (Cq); Anal. calcd for $C_8H_{13}NO_2$: C: 61.91; H: 8.44; N: 9.03. Found: C: 61.70; H: 8.35; N: 8.72.

3.2. General procedure for the *N*-alkylation of oxazolidinone 12

To a solution of oxazolidinone **12** (330 mg, 2.13 mmol) in dry DMF (8 mL) was added sodium hydride (60% wt, 102 mg, 2.55 mmol). After 10 min, the required bromo alkene (4.25 mmol) was added in one portion. The solution was stirred at rt for 0.5 h and hydrolized by addition of a saturated aqueous solution of NH_4Cl. Usual workup was followed by flash chromatography (E/PE: 8/2) and gave oxazolidinones **13**–**16** as clear oils.

3.2.1. (4*S*,5*S*)-3,4-Diallyl-5-ethyl-oxazolidin-2-one 13. Yield: 74%; R_f: 0.67 (E/PE: 7/3); $[\alpha]_D^{20}=+6.8$ (*c* 1.0, $CHCl_3$); GC (100–220°C, rate of 10°C/min): t_r=6.41 min; IR (film): 3054, 1741 cm^{-1}; ^1H NMR: 0.92 (t, *J*=7.5 Hz, 3H), 1.55–1.61 (m, 2H), 2.18–2.34 (m, 2H), 3.33–3.40 (m, 1H), 3.58 (dd, *J*=7.7 and 15.7 Hz, 1H), 4.01–4.09 (m, 1H), 4.13–4.15 (m, 1H), 5.08–5.23 (m, 4H), 5.53–5.73 (m, 2H); ^{13}C NMR: 9.3 (CH_3), 28.2, 36.6, 44.9 (CH_2), 58.9, 79.6 (CH), 118.8, 120.2 (CH_2), 131.9, 132.6 (CH), 157.8 (Cq).

3.2.2. (4*S*,5*S*)-4-Allyl-3-but-3-enyl-5-ethyl-oxazolidin-2-one 14. Yield: 42%; R_f: 0.50 (E/PE: 7/3); $[\alpha]_D^{20}=-16.6$ (*c* 0.7, $CHCl_3$); IR (film): 3019, 1734 cm^{-1}; ^1H NMR: 0.98 (t, *J*=7.5 Hz, 3H), 1.58–1.70 (m, 2H), 2.27–2.48 (m, 4H), 3.03–3.13 (m, 1H), 3.42–3.49 (m, 1H), 3.60 (td, *J*=7.7 and 14.2 Hz, 1H), 4.05–4.12 (m, 1H), 5.02–5.24 (m, 4H), 5.61–5.86 (m, 2H); ^{13}C NMR: 9.3 (CH_3), 28.2, 32.2, 36.8, 41.1 (CH_2), 59.1, 79.6 (CH), 117.8, 120.5 (CH_2), 131.9, 135.2 (CH), 158.4 (Cq).

3.2.3. (4*S*,5*S*)-4-Allyl-5-ethyl-3-pent-4-enyl-oxazolidin-2-one 15. Yield: 72%; R_f: 0.75 (E/PE: 7/3); $[\alpha]_D^{20}=-9.3$ (*c* 0.6, $CHCl_3$); ^{1}H NMR: 1.00 (t, *J*=7.5 Hz, 3H); 1.58–1.73 (m, 4H), 2.08 (q, *J*=5 Hz, 2H) 2.24–2.47 (m, 2H), 2.98–3.09 (m, 1H), 3.39–3.54 (m, 2H), 4.09 (q, *J*=5.0 Hz, 1H), 4.97–5.23 (m, 4H), 5.60–5.89 (m, 2H); ^{13}C NMR: 9.3 (CH_3), 26.9, 28.3, 31.2, 36.8, 41.6 (CH_2), 59.3, 79.5 (CH), 115.8, 120.2 (CH_2), 131.9, 137.8 (CH), 158.0 (Cq).

3.2.4. (4*S*,5*S*)-4-Allyl-5-ethyl-3-(2-methyl-allyl)-oxazolidin-2-one 16. Yield: 54%; R_f: 0.54 (E/PE: 7/3); $[\alpha]_D^{20}=-58.3$ (*c* 0.8, $CHCl_3$); ^{1}H NMR: 1.00 (t, *J*= 7.5 Hz, 3H), 1.63–1.69 (m, 2H), 1.72 (s, 3H), 2.21–2.42 (m, 2H), 3.32–3.39 (m, 1H), 3.54 (d, *J*=17.5 Hz, 1H), 4.08–4.15 (m, 2H), 4.90 (s, 1H), 4.95 (s, 1H), 5.14–5.22 (m, 2H), 5.59–5.75 (m, 1H); ^{13}C NMR: 9.4, 20.3 (CH_3), 28.5, 36.5, 48.3 (CH_2), 58.8, 79.6 (CH), 114.3, 120.2 (CH_2), 131.9 (CH) 140.2, 158.1 (Cq).

3.3. General procedure for the metathesis of diolefinic oxazolidinones 13–16

To a solution of oxazolidinone (1.13 mmol) in dichloromethane (20 mL) was added Grubbs' catalyst (23 mg, 2.5% molar ratio). After 2 h of reflux, the solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (E/PE: 4/6). Bicyclic oxazolidinones **17**–**20** were obtained as oils.

3.3.1. (1*S*,4*S*)-1-Ethyl-1,5,8,8a-tetrahydro-oxazolo[3,4-*a*]-pyridin-3-one 17. Yield: 79%; R_f: 0.39 (E/PE: 7/3); GC (100 to 220°C, rate 10°C/min): tr 6.73 min (98%); $[\alpha]_D^{20}=+3$ (*c* 0.5, $CHCl_3$); IR (film): 3020, 1744 cm^{-1}; ^{1}H NMR: 0.96 (t, *J*=7.0 Hz, 3H), 1.65–1.78 (m, 2H), 2.14–2.23 (m, 2H), 3.34 (quint., *J*=7.0 Hz, 1H), 3.56–3.65 (m, 1H), 3.98–4.08 (m, 2H), 5.69–5.78 (m, 2H); ^{13}C NMR: 9.4 (CH_3), 27.7, 30.4, 41.2 (CH_2), 55.5, 83.1, 125.5, 124.2 (CH), 157.4 (Cq); MS (EI, 70 eV): *m/z* 167 (M^+, 40), 122 (30), 108 (44), 95 (30), 80 (41), 54 (100); Anal. calcd for $C_9H_{13}O_2N$, C, 64.65; H, 7.84; N, 8.33. Found. C, 65.04; H, 7.72; N, 8.02.

3.3.2. (1*S*,4*S*)-1-Ethyl-5,6,9,9a-tetrahydro-oxazolo[3,4-*a*]-azepin-3-one 18. Yield: 80%; R_f: 0.36 (E/PE: 7/3); $[\alpha]_D^{20}=-85.2$ (*c* 0.3, $CHCl_3$); ^{1}H NMR: 1.02 (t, *J*= 7.0 Hz, 3H), 1.64–1.76 (m, 2H), 2.17–2.41 (m, 4H), 2.81–2.92 (m, 1H), 3.24–3.32 (m, 1H), 3.85–3.98 (m, 2H), 5.78–5.97 (m, 2H); ^{13}C NMR: 9.2 (CH_3), 27.3, 28.8, 34.9, 42.8 (CH_2), 60.5, 80.9, 128.1, 132.7 (CH), 157.5 (Cq).

3.3.3. (1*S*,4*S*)-1-Ethyl-1,4,5,6,9a-hexahydro-2-oxa-3a-aza-cyclopentacycloocten-3-one 19. Yield: 86%; R_f: 0.36 (E/PE: 7/3); $[\alpha]_D^{20}=-55.5$ (*c* 0.3, $CHCl_3$); IR (film): 3010, 1729 cm^{-1}; ^{1}H NMR: 1.01 (t, *J*=7.5 Hz, 3H), 1.42–1.56 (m, 1H), 1.60–1.77 (m, 2H), 1.93–2.14 (m, 2H), 2.17–2.37 (m, 3H), 2.72–2.85 (m, 1H), 3.28 (q, *J*=5.8 Hz, 1H), 3.77 (ddd, *J*=14.5, 4.6 and 2.4 Hz, 1H), 4.00 (q, *J*=6.5 Hz, 1H), 5.64–5.92 (m, 2H); ^{13}C NMR: 8.6 (CH_3), 26.4, 26.6, 27.4, 31.7, 41.3 (CH_2), 63.3, 78.6, 124.4, 133.5 (CH), 158.5 (Cq).

3.3.4. (1*S*,4*S*)-1-Ethyl-6-methyl-1,5,8,8a-tetrahydro-oxazolo[3,4-*a*]pyridin-3-one 20. Yield: 74%; R_f: 0.56 (E/PE: 8/2); $[\alpha]_D^{20}=-161.9$ (*c* 0.3, $CHCl_3$); IR (film): 3015, 1749 cm^{-1}; ^{1}H NMR: 0.95 (t, *J*=7.5 Hz, 3H), 1.60–1.73 (m, 4H), 2.10 (s, 3H), 3.29 (quint., *J*=4.9 Hz, 1H), 3.45 (d, *J*=15.0 Hz, 1H), 3.89 (d, *J*=15.0 Hz, 1H), 4.02 (q, *J*= 7.1 Hz, 1H), 5.40–5.44 (m, 1H); ^{13}C NMR: 9.4, 20.7 (CH_3), 27.8, 30.4, 44.7 (CH_2), 55.5, 83.0, 118.0, 131.5 (CH), 157.2 (Cq).

3.3.5. (1*S*,4*S*,6*R*,7*S*)-1-Ethyl-6,7-dihydroxy-hexahydro-oxazolo[3,4-*a*]pyridin-3-one 21. To a solution of **17** (79 mg, 0.47 mmol) in a (1/8) mixture of water and acetone (2 mL) and cooled at −20°C was added an aqueous solution of osmium tetroxide (4% wt. solution, 0.6 mL, 0.024 mmol) and *N*-methyl morpholine *N*-oxide (110 mg, 0.95 mmol). The reaction medium was warmed to rt (0.5 h) and quenched by addition of sodium thiosulfate (23 mg). The mixture was then saturated with sodium chloride and extracted thouroughly with dichloromethane. Drying of the organic layer over $MgSO_4$ and concentration under reduced pressure gave a residue that was purified by flash chromatography (E/EtOH:9/1). Diol **21** was obtained as a white solid (43 mg, 45%). Slow evaporation of a methanolic solution gave crystals. R_f: 0.33 (E/EtOH: 9/1); mp: 165–168°C; $[\alpha]_D^{20}=-3.5$ (*c* 0.06, MeOH) ^{1}H NMR (CD_3OD): 0.90 (t, *J*=7.5 Hz, 3H), 1.46–1.68 (m, 3H), 1.93 (td, *J*=3.6 and 13.6 Hz, 1H), 2.90–3.05 (m, 1H), 3.44–3.61 (m, 3H), 3.92–3.95 (m, 1H), 3.97 (q, *J*=6.1 Hz, 1H); ^{13}C NMR (CD_3OD): 9.6 (CH_3), 28.6, 37.4, 42.6 (CH_2), 55.0, 68.9, 69.0, 83.5 (CH), 157.1 (Cq). Crystal data:[10] $C_9H_{15}NO_4$, orthorhombic, no centrosymmetric $P2_1$ space group, Z=4, D_c=1.41 g/cm^3, μ (Mo Kα)=1.04 cm^{-1}, a=5.1132(8) Å, b=110.332(2) Å, c=16.336(2) Å, b=90°, V=947.9(3) Å^3. The final refinement of 129 variables using 1620 reflexions (with $(Fo)^2>3\sigma(Fo)^2$) were used to solve the structure to R=0.0444 and R_w=0.0517.

3.3.6. (1*S*,4*S*)-1-Ethyl-hexahydro-oxazolo[3,4-*a*]pyridin-3-one 23. A suspension of **17** (81 mg, 0.48 mmol) and palladium on carbon (20% wt., 30 mg) in ethanol (7 mL) was vigorously stirred under an hydrogen atmosphere for 2 h. Filtration over a pad of Celite and concentration under reduced pressure gave title compound as an oil (75 mg, 92%). R_f: 0.50 (E); $[\alpha]_D^{20}=-33.2$ (*c* 0.4, $CHCl_3$); IR (film): 1740 cm^{-1}; ^{1}H NMR: 1.01 (t, *J*=7.5 Hz, 3H), 1.24–1.93 (m, 8H), 2.80 (td, *J*=3.4 and 12.6 Hz, 1H), 3.19–3.28 (m, 1H), 3.81–3.88 (m, 1H), 4.00 (q, *J*= 6.5 Hz, 1H); ^{13}C NMR: 9.4 (CH_3), 23.0, 24.7, 27.4, 31.0, 41.5 (CH_2), 59.8, 82.2 (CH), 157.3 (Cq).

3.3.7. (1*S*,2*S*)-Piperidin-2-yl-propan-1-ol ((−)-β-conhydrine) 1. To a solution of 23 (66 mg, 0.39 mmol) in 2 mL of ethanol and 2 mL of water was added lithium hydroxide (115 mg, 2.7 mmol). After 5 h of reflux, the mixture was concentrated under reduced pressure, the residue was taken up in water and ether. Usual workup gave an oil that crystallized on standing (25 mg, 45%). R_f: 0.05 (E); $[\alpha]_D^{20}=-34.1$ (*c* 0.4, $CHCl_3$); mp: 67°C (Lit.[2a]: 72°C), ^{1}H NMR: 0.92 (t, *J*=7.5 Hz, 3H), 1.02–1.50 (m, 8H), 2.29 (ddd, *J*=2.5, 7.5 and 10.0 Hz, 1H), 2.52 (td, *J*=2.7 and 11.7 Hz, 1H), 2.98–3.05 (m, 1H), 3.15 (td, *J*=3.4 and

7.7 Hz, 1H); ^{13}C NMR: 10.5 (CH_3), 24.8, 26.8, 26.9, 29.5, 46.9 (CH_2), 61.3, 75.9 (CH).

3.3.8. (1*S*,4*S*)-1-(1,2,3,6-tetrahydro-pyridin-2-yl)-propan-1-ol 24. Following the above procedure and starting with **17** (67 mg, 0.40 mmol), title compound was obtained as an oil that cristallyzed on standing (31 mg, 54%). R_f: 0.05 (E); $[\alpha]_D^{20}=-37.5$ (*c* 0.6, $CHCl_3$); mp: 65–66°C, ^{1}H NMR: 0.93 (t, *J*=7.5 Hz, 3H), 1.18–1.37 (m, 1H), 1.46–1.64 (m, 1H), 1.73–1.83 (m, 1H), 1.90–1.99 (m, 1H), 2.47–2.56 (m, 1H), 2.72 (bs, 2H), 3.17 (td, *J*=3.1 and 8.0 Hz, 1H), 3.30 (bs, 2H), 5.69 (bs, 2H); ^{13}C NMR: 10.1 (CH_3), 26.4, 28.3, 45.3 (CH_2), 57.6, 75.7, 125.3, 127.7 (CH).

3.3.9. (1*S*,4*S*,6*RS*)-1-Ethyl-6-methyl-hexahydro-oxazolo-[3,4-*a*]pyridin-3-one 22. Following the procedure reported above for the hydrogenation of **17**, title compound was prepared from **20** (25 mg, 0.138 mmol) and was obtained as an oil (22 mg, 88%). This compound consisted in a 86/14 mixture of stereoisomers at C_6. R_f: 0.46 (E/PE: 8/2); ^{1}H NMR (major stereoisomer): 0.95–0.99 (m, 6H), 1.54–1.73 (m, 6H), 1.90–1.96 (bm, 1H), 3.91 (dd, *J*=4 and 13.2 Hz, 1H), 3.09–3.17 (m, 1H), 3.50 (d, *J*=13.0 Hz, 1H), 3.95 (q, *J*=6.5 Hz, 1H); ^{13}C NMR: 9.5, 16.7 (CH_3), 25.4 (CH_2), 27.0 (CH), 27.6, 28.8, 46.7 (CH_2), 60.4, 82.4 (CH) 157.8 (Cq). The amount of minor stereoisomer was determined by ^{1}H NMR on the following resonance: 2.97 (dd, *J*=3.5 and 13.0 Hz, 0.14H).

3.3.10. (4*S*,2*S*)-4-Benzyl-oxazolidine-2,3-dicarboxylic acid-3-*tert*-butyl ester 26. Following the procedure reported[6] for the preparation of **5**, and starting with (*S*)-phenylalaninol **25** (3.5 g, 23.1 mmol), title compound **26** was obtained as a white solid (5.45 g, 77%): $[\alpha]_D^{20}=-95.1$ (*c* 0.9, $CHCl_3$); mp 142°C; IR (nujol): 3163, 1751, 1638 cm^{-1}; ^{1}H NMR: 1.36 (bs, 9H), 2.71 (dd, *J*=8.7 and 13.2 Hz, 1H), 3.07 (bs, 1H), 3.84–4.28 (m, 3H), 5.39 (bs, 1H), 7.12–7.27 (m, 5H), 9.34 (bs, 1H); ^{13}C NMR: 28.5 (CH_3), 39.7, (CH_2), 58.6 (CH), 72.6 (CH_2), 82.6, 127.2, 129.1, 129.7 (CH), 137.7, 157.0, 171.0 (Cq).

3.3.11. (4*S*,2*S*)-4-Benzyl-2-(methoxy-methyl-cabamoyl)-oxazolidine-3-carboxylic acid-3-*tert*-butyl ester 27. Following the procedure reported[6] for the preparation of Weinreb amide **5**, and starting with **26** (5.45 g, 17.7 mmol), title compound was obtained as a white solid (4.9 g, 79%): $[\alpha]_D^{20}=-36.5$ (*c* 0.4, $CHCl_3$); mp: 103–104°C; IR (nujol): 1956, 1889, 1715 cm^{-1}; ^{1}H NMR: 1.38 (bs, 9H), 2.79 (broad dd, *J*=10.5 and 12.5 Hz, 1H), 3.20 (bs, 3H), 3.28–3.50 (bm, 1H), 3.73 (bs, 3H), 3.92 (bs, 2H),,4.09 (bs, 1H), 5.79 and 5.92 (two bs, 1H), 7.13–7.21 (m, 5H); ^{13}C NMR: 27.8, 31.7 (CH_3), 39.0 (broadened) (CH_2), 59.0 (broadened) (CH), 61.4 (CH_3), 80.3 (Cq), 83.0, 125.8, 128.0, 129.7 (CH), 137.7, 157.0 (broadened) (Cq). MS (EI, 70 eV): *m*/*z* 251 (13), 206 (100), 162 (70), 117 (50), 91 (26), 57 (55); Anal. calcd for $C_{18}H_{26}O_5N_2$, C, 61.70; H, 7.48; N, 7.99. Found. C, 61.95; H, 7.75; N, 7.97.

3.3.12. (4*S*,2*S*)-4-Benzyl-2-propionyl-oxazolidine-3-carboxylic acid-3-*tert*-butyl ester 28. To a solution of Weinreb amide **27** (987 mg, 2.82 mmol) in ether (10 mL) and cooled to 0°C, was added dropwise a solution of ethylmagnesium bromide (3N solution in ether, 1.4 mL, 4.23 mmol). The reaction mixture was then stirred at rt for 1 h, and hydrolyzed by addition of a saturated aqueous solution of NH_4Cl. Usual workup gave a residue that was purified by flash chromatography (E/PE: 2/8). Title compound was obtained as an oil (650 mg, 72%). R_f: 0.60 (E/PE: 2/8); $[\alpha]_D^{20}=-73.8$ (*c* 0.8, $CHCl_3$); IR (film): 3020, 2925, 2881, 1811, 1711 cm^{-1}; ^{1}H NMR: 1.15 (t, *J*=7.5 Hz, 3H), 1.51 (s, 9H), 2.55–2.85 (m, 3H), 3.41 (bs, 1H), 3.98 (bs, 2H), 4.21 (bs, 1H), 5.26 and 5.43 (two bs, 1H), 7.27–7.40 (m, 5H); ^{13}C NMR: 7.6, 28.6 (CH_3), 32.0 (broadened), 39.5 (broadened) (CH_2), 58.5 (CH), 66.2 (broadened) (CH_2), 81.6 (Cq), 89.6, 127.0, 129.0, 129.7 (CH), 138.1, 153.2, 206.1 (Cq); MS (CI, NH_3): *m*/*z* 246 (8), 220 (MH^+, $-CO_2$, $-C_4H_8$, 69), 206 (77), 162 (100), 117 (68), 91 (26).

3.3.13. (2*S*,4*S*,9*S*)-4-Benzyl-2-(1-hydroxy-propyl)-oxazolidine-3-carboxylic acid *tert*-butyl ester 29a and (2*S*,4*S*,9*R*)-4-benzyl-2-(1-hydroxy-propyl)-oxazolidine-3-carboxylic acid *tert*-butyl ester 29b. Following the procedure described for the reduction of **6**, and starting with **28** (3.1 g, 9.7 mmol), title compound **29a** was obtained as an oil (2.3 g, 72%) after purification by flash chromatography (E/PE: 5/95 and then 12/88). Minor stereoisomer **29b** was eluted in second (306 mg, 10%). Compound **29a**: R_f: 0.66 (E/PE: 4/6), $[\alpha]_D^{20}=-53.8$ (*c* 0.7, $CHCl_3$); IR (film): 3415, 2978, 2946, 1684, 1391 cm^{-1}; ^{1}H NMR: 0.96 (t, *J*=7.5 Hz, 3H), 1.34 (s, 9H), 1.56–1.75 (m, 2H), 2.62 (dd, *J*=8.7 and 13.0 Hz, 1H), 2.96 (dd, *J*=13.0 and 5.0 Hz, 1H), 3.45–3.54 (m, 1H), 3.70 (dd, *J*=6.2 and 8.9 Hz, 1H), 3.79 (dd, *J*=2.8 and 8.6 Hz, 1H), 4.02–4.15 (m, 1H), 4.88 (d, *J*=6.7 Hz, 1H), 7.10–7.23 (m, 5H); ^{13}C NMR: 9.8 (CH_3), 26.1 (CH_2), 28.7 (CH_3), 40.5 (CH_2), 59.1 (CH), 70.3 (CH_2), 76.6 (CH), 81.4 (Cq), 92.5, 127.0, 129.0, 129.0 (CH), 137.7, 158.6 (Cq). Compound **29b**: R_f: 0.58 (E/PE: 4/8), mp: 65°C; $[\alpha]_D^{20}=-81.4$ (*c* 0.7, $CHCl_3$); IR (nujol): 3383, 3010, 2920, 1672 cm^{-1}; ^{1}H NMR: 0.70 (t, *J*=7.5 Hz, 3H), 1.40 (s, 9H), 1.50–1.60 (bm, 2H), 2.67 (bt, *J*=9.1 Hz, 1H), 2.95 (bs, 1H), 3.02 (dd, *J*=4.0 and 9.1 Hz, 1H), 3.50–4.10 (m, 4H), 4.95 (bs, 1H), 7.05–7.30 (m, 5H); ^{13}C NMR: 10.8 (CH_3), 25.8 (CH_2), 28.7 (CH_3), 40.4 (CH_2), 59.0 (broadened) (CH), 70.0 (CH_2), 73.0 (CH), 81.4 (Cq), 92.5, 127.0, 129.0, 129.0 (CH), 137.7, 158.6 (Cq); Anal. calcd for $C_{18}H_{27}O_4N$, C, 67.26; H, 8.47; N, 4.36. Found C, 67.26; H, 8.53; N, 4.25.

When $CeCl_3$, $7H_2O$ (1.5 equiv.) was added to the reaction mixture, prior to the addition of sodium borohydride, the produced ratio of **29a** and **29b** was 24/76, and compound **29b** was isolated pure after flash chromatography, with a 54% yield.

3.3.14. (3*S*,6*S*,7*S*)-3-Benzyl-6-ethyl-tetrahydro-1,5-dioxa-3a-aza-pentalen-4-one 30. Following the procedure described for the preparation of **8**, with a time of reflux of 0.5 h, and starting with **29a** (470 mg, 1.46 mmol), title compound was obtained as a white solid (258 mg, 71%) after flash chromatography (E/PE: 15/85); R_f: 0.36 (E/PE: 4/6); mp: 65°C; $[\alpha]_D^{20}=-21.2$ (*c* 0.6, $CHCl_3$); IR (nujol): 2973, 2937, 2870, 1761, 1684 cm^{-1}; ^{1}H NMR: 1.26 (t, *J*=7.5 Hz, 3H); 1.88–2.08 (m, 2H), 3.13 (dd, *J*=11.2 and 15.2 Hz, 1H), 3.87 (t, *J*=7.7 Hz, 1H), 4.00–4.18 (m, 3H), 4.55 (td, *J*=6.7 and 1.7 Hz, 1H), 5.09 (d, *J*=1.7 Hz, 1H), 7.43–7.57 (m, 5H); ^{13}C NMR: 9.2 (CH_3), 26.4, 34.2

(CH_2), 60.8 (CH), 71.4 (CH_2), 81.6, 95.1, 127.2, 129.2, 129.3 (CH), 138.4, 158.7 (Cq); Anal. calcd for $C_{14}H_{17}NO_3$: C: 68.00; H: 6.93; N: 5.66. Found: C: 68.15; H: 7.07; N: 5.61.

3.3.15. (3*S*,6*S*,7*R*)-3-Benzyl-6-ethyl-tetrahydro-1,5-dioxa-3a-aza-pentalen-4-one 31. Following the procedure described for the preparation of **8**, with a time of reflux of 0.5 h, and starting with **29b** (319 mg, 0.99 mmol), title compound was obtained as a white solid (220 mg, 90%) after flash chromatography (E/PE: 15/85); R_f: 0.58 (E/PE: 4/6); mp: 70°C; $[\alpha]_D^{20}=+9.3$ (*c* 1.0, $CHCl_3$); IR (film): 3019, 2973, 2870, 1761, 1684 cm^{-1}; ^1H NMR: 0.94 (t, *J*=7.5 Hz, 3H); 1.69–1.82 (m, 2H), 2.85 (dd, *J*=10.5 and 15.5 Hz, 1H), 3.48 (t, *J*=7.5 Hz, 1H), 3.68–3.82 (m, 3H), 4.33 (bq, *J*=5.0 Hz, 1H), 5.05 (d, *J*=4.8 Hz, 1H), 7.40–7.55 (m, 5H); ^{13}C NMR: 10.1 (CH_3), 22.2, 34.0 (CH_2), 61.7 (CH), 71.3 (CH_2), 91.9, 127.0, 127.2, 129.1 (CH), 138.5, 158.9 (Cq); MS (CI, NH_3): *m/z* 248 (MH^+, 27), 134 (17), 100 (65), 88 (84), 71 (100).

3.3.16. (4*S*,5*S*,6*S*)-4-Allyl-3-(1-benzyl-2-hydroxy-ethyl)-5-ethyl oxazolidin-2-one 32. Following the procedure reported for the preparation of **9**, and starting with **30** (239 mg, 0.97 mmol), title compound was obtained as a white solid (238 mg, 85%) after flash chromatography (E/PE: 9/1); R_f: 0.68 (E); mp: 76°C; $[\alpha]_D^{20}=-87.4$ (*c* 0.9, $CHCl_3$); IR (nujol): 3430, 1709 cm^{-1}; ^1H NMR: 1.01 (t, *J*=7.5 Hz, 3H); 1.29–1.60 (m, 2H), 2.39–2.67 (m, 2H), 2.88–3.00 (m, 1H), 3.20 (dd, *J*=5.5 and 13.5 Hz, 1H), 3.52 (dd, *J*=10.2 and 13.5 Hz, 1H), 3.65–3.88 (m, 1H), 4.06–4.32 (m, 4H), 5.24–5.46 (m, 2H), 5.72–5.93 (m, 1H), 7.43–7.61 (m, 5H); ^{13}C NMR: 9.3 (CH_3), 28.0, 34.7, 37.8 (CH_2), 59.2, 62.5 (CH), 64.8 (CH_2), 80.7 (CH), 120.3 (CH_2), 127.1, 129.1, 129.7, 131.9 (CH),138.7, 157.5 (Cq); MS (CI, NH_3): *m/z* 290 (MH^+,19), 248 (87), 230 (15), 209 (24), 198 (70), 178 (10), 154 (26), 114 (26), 91 (100); Anal. calcd for $C_{17}H_{23}NO_3$ (0.5 H_2O): C: 68.45; H: 8.05; N: 4.69. Found: C: 68.67; H: 7.97; N: 4.65.

3.3.17. (4*R*,5*R*,6*S*)-4-Allyl-3-(1-benzyl-2-hydroxy-ethyl)-5-ethyl oxazolidin-2-one 33. Following the procedure reported for the preparation of **9**, and starting with **31** (161 mg, 0.65 mmol), title compound was obtained as an oil (123 mg, 65%) after flash chromatography (E/PE: 1/1); R_f: 0.42 (E); $[\alpha]_D^{20}=-33.1$ (*c* 0.1, $CHCl_3$); IR (film): 3404, 1730 cm^{-1}; ^1H NMR: 0.83 (t, *J*=7.5 Hz, 3H); 1.30–1.47 (m, 2H), 1.73–1.86 (m, 1H), 2.02–2.13 (m, 1H), 2.35–2.45 (m, 1H), 3.05 (dd, *J*=3.5 and 7.3 Hz, 1H), 3.30–3.37 (m, 1H), 3.58–3.68 (m, 1H), 3.68–3.78 (m, 1H), 3.90–3.97 (m, 2H), 4.97–5.08 (m, 2H), 5.35–5.45 (m, 1H), 7.18–7.30 (m, 5H); ^{13}C NMR: 8.5 (CH_3), 27.5, 34.2, 37.4 (CH_2), 58.1, 60.7, 63.2, 79.8 (CH), 119.8 (CH_2), 126.5, 128.4, 129.0, 131.8 (CH),138.2, 157.8 (Cq).

3.3.18. (2*S*,4*S*,5*S*)-2-(4-Allyl-5-ethyl-2-oxo-oxazolidin-3-yl)-3-phenyl-propionaldehyde 34. To a solution of alcohol **32** (137 mg, 0.48 mmol) in dichloromethane (7 mL) was added Dess–Martin periodinane (307 mg, 0.72 mmol). The suspension was stirred for 1 h at rt, and ether (20 mL) was added. The suspension was then treated with a (1/1) mixture of saturated aqueous solution of $NaHCO_3$ and saturated aqueous solution of $Na_2S_2O_3$ (10 mL). Usual workup then gave aldehyde **34** as a solid that was not further purified (138 mg), R_f: 0.63 (AcOEt/PE: 1/1), mp: 104–105°C, $[\alpha]_D^{20}=-136.8$ (*c* 0.3, $CHCl_3$); IR (Nujol): 2968, 2920, 2848, 1733 cm^{-1}; ^1H NMR: 0.70 (t, *J*=7.5 Hz, 3H), 1.02–1.32 (m, 2H), 2.11–2.24 (m, 2H), 2.52 (bq, *J*=5.0 Hz, 1H), 3.12–3.33 (m, 2H), 3.75 (dd, *J*=5 and 11 Hz, 1H), 3.93 (bq, *J*=5.2 Hz, 1H), 5.00–5.12 (m, 2H), 5.40–5.60 (m, 1H), 7.12–7.29 (m, 5H), 9.66 (s, 1H); ^{13}C NMR: 8.8 (CH_3), 27.4, 33.0, 37.2 (CH_2), 60.9, 63.2, 80.9 (CH) 120.2 (CH_2), 127.3, 128.9, 129.2, 131.3 (CH), 137.2, 157.1 (Cq), 198.3 (CH).

3.3.19. (2*S*,4*S*,5*R*)-2-(4-Allyl-5-ethyl-2-oxo-oxazolidin-3-yl)-3-phenyl-propionaldehyde 35. Following the above procedure and starting with **33** (123 mg, 0.43 mmol), aldehyde **35** was obtained as an oil that was not further purified (103 mg), R_f: 0.43 (AcOEt/PE: 4/6), $[\alpha]_D^{20}=-50.7$ (*c* 0.1, $CHCl_3$); ^1H NMR: 0.74 (t, *J*=7.5 Hz, 3H), 1.18–1.36 (m, 2H), 1.75–1.87 (m, 1H), 1.91–2.01 (m, 1H), 3.07 (dd, *J*=11.4 and 15.1 Hz, 1H), 3.19–3.26 (m, 1H), 3.40 (dd, *J*=5.2 and 15.1 Hz, 1H), 3.93–4.00 (m, 1H), 4.32 (dd, *J*=5.2 and 11.4 Hz, 1H), 4.94–5.07 (m, 2H), 5.26–5.46 (m, 1H), 7.15–7.29 (m, 5H), 9.67 (s, 1H); ^{13}C NMR: 9.1 (CH_3), 27.9, 30.1, 32.4 (CH_2), 59.5, 63.4, 80.7 (CH) 120.4 (CH_2), 127.5, 129.2, 131.6 (CH), 136.7, 158.2 (Cq), 199.1 (CH).

3.3.20. (4*S*,5*S*,6*S*)-4-Allyl-3-(1-benzyl-allyl)-5-ethyl oxazolidin-2-one 36. To a suspension of triphenylmethylphosphonium bromide (388 mg, 1.09 mmol) in THF (7 mL), cooled at −78°C, was added dropwise butyllithium (1.6N solution in hexanes, 0.68 mL, 1.02 mmol). The reaction mixture was warmed to rt and then recooled at −30°C. Crude aldehyde **34** (142 mg, 0.49 mmol), in THF (7 mL) was then added dropwise. The resulting white suspension was warmed to rt (1 h), and hydrolized by addition of a saturated aqueous solution of NH_4Cl (10 mL). Usual workup gave an oil that was purified by flash chromatography (AcOEt/PE: 7/93) to afford title compound as a white solid (113 mg, 80%): R_f: 0.37 (AcOEt/PE: 2/8), mp: 68–70°C; IR (Nujol): 3063, 2925, 1735, 1639 cm^{-1}; $[\alpha]_D^{20}=-15.5$ (*c* 0.5, $CHCl_3$); ^1H NMR: 0.67 (t, *J*=7.5 Hz, 3H), 0.80–1.15 (m, 2H), 2.12–2.23 (m, 2H), 2.62–2.70 (m, 1H), 2.83 (dd, *J*=6.0 and 13.5 Hz, 1H), 3.39 (dd, *J*=10.2 and 13.7 Hz, 1H), 3.79–3.83 (m, 2H), 4.94–5.18 (m, 4H), 5.42–5.58 (m, 1H), 6.08–6.22 (m, 1H), 7.14–7.22 (m, 5H); ^{13}C NMR: 9.2 (CH_3), 28.0, 38.1, 38.7 (CH_2), 59.8, 62.5, 79.6 (CH) 117.2, 120.1 (CH_2), 127.7, 129.6, 130.4, 132.8,137.3 (CH), 139.3 157.1 (Cq); Anal. calcd for $C_{18}H_{23}NO_2$: C: 75.76; H: 8.12; N: 4.91. Found: C: 75.56; H: 8.44; N: 4.45.

3.3.21. (4*R*,5*R*,6*S*)-4-Allyl-3-(1-benzyl-allyl)-5-ethyl oxazolidin-2-one 37. Following the above procedure and starting with **34** (108 mg, 0.38 mmol) title compound was obtained as a white solid (40 mg, 37%): R_f: 0.43 (AcOEt/PE: 2/8), mp: 45–47°C; IR (Nujol): 1735 cm^{-1}; $[\alpha]_D^{20}=-29.2$ (*c* 1.0, $CHCl_3$); ^1H NMR: 0.76 (t, *J*=7.5 Hz, 3H), 1.14–1.37 (m, 2H), 1.83–1.97 (m, 1H), 2.04–2.17 (m, 1H), 3.05 (dd, *J*=6.2 and 14.1 Hz, 1H), 3.17–3.23 (m, 1H), 3.25 (dd, *J*=10.1 and 14.1 Hz, 1H), 3.88 (td, *J*=10.5 and 5.5 Hz, 1H), 4.11–4.24 (m, 1H), 5.00–5.21 (m, 4H), 5.29–5.47 (m, 1H), 6.01 (ddd, *J*=7.0, 10.5 and 17.2 Hz, 1H),

7.11–7.30 (m, 5H); ^{13}C NMR: 9.1 (CH_3), 27.9, 37.8, 38.0 (CH_2), 58.2, 59.4, 79.7 (CH) 117.4, 119.8 (CH_2), 127.1, 128.9, 129.5, 132.3,136.7 (CH), 139.7 157.4 (Cq).

3.3.22. (1*S*,4*S*,5*S*)-5-Benzyl-1-ethyl-1,5,8,8a-tetrahydro-oxazolo[3,4-*a*]pyridin-3-one 38. Following the procedure described for the metathesis of **13**–**16** and starting with **36** (20 mg, 0.07 mmol), title compound was obtained after flash chromatography (AcOEt/PE: 5/95), as an oil that crystallized on standing (15 mg, 83%): R_f: 0.43 (E); mp: 98–100°C; $[\alpha]_D^{20}$=+99.3 (*c* 0.7, $CHCl_3$); IR (film): 2972, 1739, 1162 cm^{-1}; ^{1}H NMR: 0.96 (t; *J*=7.5 Hz, 3H), 1.37–1.49 (m, 2H), 1.57–1.75 (m, 1H), 1.94–2.08 (m, 1H), 3.13 (dd, *J*=3.0 and 13.0 Hz, 1H), 3.20–3.35 (m, 2H), 3.78 (ddd, *J*=5.5, 7.0 and 10.0 Hz, 1H), 4.16–4.26 (m, 1H), 5.55 (td, *J*=3.1 and 10.2 Hz, 1H), 5.69 (ddt, *J*=1.5, 6.8 and 10.2 Hz, 1H), 7.07–7.24 (m, 5H); ^{13}C NMR: 9.9 (CH_3), 26.2, 28.8, 38.5 (CH_2), 53.8, 58.8, 82.6, 123.8, 126.8, 128.2, 128.6, 130.7 (CH), 135.8, 156.4 (Cq).

3.3.23. (1*S*,4*S*,5*R*)-5-Benzyl-1-ethyl-1,5,8,8a-tetrahydro-oxazolo[3,4-*a*]pyridin-3-one 39. Following the procedure described for the metathesis of **13**–**16** and starting with **37** (35 mg, 0.101 mmol), title compound was obtained after flash chromatography (AcOEt/PE: 5/95), as an oil (23 mg, 74%): R_f: 0.54 (AcOEt/PE: 4/6); $[\alpha]_D^{20}$=+267.8 (*c* 0.2, $CHCl_3$); IR (film): 3015, 2962, 1749, 1649, 1601, 1500, 1415 cm^{-1}; ^{1}H NMR: 0.85 (t, *J*=7.5 Hz, 3H), 1.38–1.65 (m, 2H), 1.80–2.05 (m, 2H), 2.68–2.80 (m, 1H), 2.85–3.00 (m, 2H), 3.90 (bq, *J*=5.7 Hz, 1H), 4.32–4.42 (m, 1H), 5.64 (td, *J*=2.2 and 10.7 Hz, 1H), 5.65–5.70 (m, 1H), 7.08–7.25 (m, 5H); ^{13}C NMR: 8.9 (CH_3), 27.4, 29.7, 39.6 (CH_2), 51.4, 53.1, 82.5, 123.7, 126.6, 127.8, 128.2, 129.9 (CH), 136.8, 157.4 (Cq); Anal. calcd for $C_{16}H_{19}NO_2$: C: 74.68; H: 7.44; N: 5.44. Found: C: 73.88; H: 7.63; N: 5.26.

References

1. Casiraghi, G.; Zanardi, F.; Rassu, G.; Spanu, P. *Chem. Rev.* **1995**, *95*, 1677–1716.
2. For asymmetric syntheses of β-conhydrine see: (a) Ratovelomanana, V.; Royer, J.; Husson, H. P. *Tetrahedron Lett.* **1985**, *32*, 3803–3806. (b) Comins, D. L.; Williams, A. L. *Tetrahedron Lett.* **2000**, *41*, 2839–2842.
3. For an asymmetric synthesis of (−)-methyl palustramate, see: Angle, S. R.; Henry, R. M. *J. Org. Chem.* **1998**, *63*, 7490–7497.
4. Elbein, A. D.; Molyneux, R. J. *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 5, pp 1–54.
5. Preliminary communication: Agami, C.; Couty, F.; Rabasso, N. *Tetrahedron Lett.* **2000**, *41*, 4113–4116.
6. Agami, C.; Couty, F.; Lam, H.; Mathieu, H. *Tetrahedron* **1998**, *54*, 8783–8796.
7. For some examples of RCM applied to the synthesis of nitrogen heterocycles see (a) Philips, A. J.; Abell, A. D. *Aldrichim. Acta* **1999**, *32*, 75–89. (b) Eunyoung, J.; Yongim, N.; Sukbok, C. *Tetrahedron Lett.* **1999**, *40*, 5581–5582. (c) Sauers, A. J.; Ellman, J. A. *J. Org. Chem.* **2000**, *65*, 1222–1224. (d) Wallace, D. J.; Cowden, C. J.; Kennedy, D. J.; Ashwood, M. S.; Cottrell, I. F.; Dolling, U. H. *Tetrahedron Lett.* **2000**, *41*, 2027–2029. (e) Lennartz, M.; Steckhan, E. *Tetrahedron* **2001**, *57*, 675–680.
8. Agami, C.; Amiot, F.; Couty, F.; Dechoux, L.; Kaminsky, C.; Venier, O. *Tetrahedron: Asymmetry* **1998**, *9*, 3955–3958.
9. Analogous problems of epimerization were observed in the course of a synthesis of castanospermine using this olefination/RCM sequence: Overkleeft, H. S.; Pandit, U. K. *Tetrahedron Lett.* **1996**, *37*, 547–550.
10. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, and copies can be obtained, free of charges, by quoting the publication citation 5.