

Substrate-controlled Crotylboration† from *N*-(*tert*-Butoxycarbonyl)amino Aldehydes

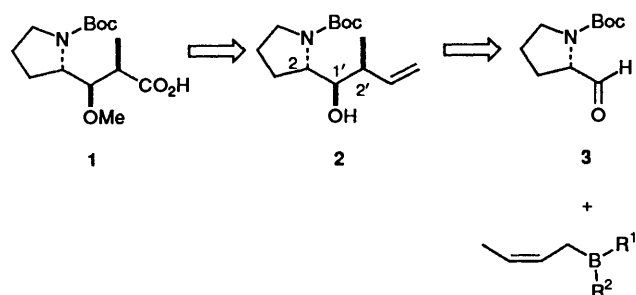
Gilles Niel,* Florence Roux, Ysadora Maisonnasse, Isabelle Maugras, Joël Poncet and Patrick Jouin

UPR 9023 CNRS-Centre CNRS-INSERM, rue de la Cardonille, F-34094 Montpellier Cedex 5, France

Chiral or achiral (*Z*)-crotylorganoboron compounds add preferentially *anti* to *N*-(*tert*-butoxycarbonyl)-amino aldehydes. *N*-(*tert*-Butoxycarbonyl)prolinal **3** presents a remarkably high diastereofacial selectivity. Double stereodifferentiation, starting from compound **3**, allows complete diastereoselective access to the γ -amino- β -hydroxy- α -methyl acid dolaproine **1** present in the antiproliferative dolastatin **10**.

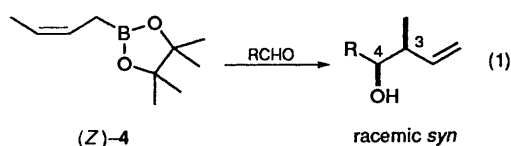
The α -amino aldehydes, derived from natural α -amino acids, play an important role in organic synthesis¹ as precursors of more elaborate chiral molecules. Indeed, the presence of a chiral centre in the α -position of an α -amino aldehyde as well as the nature of the nitrogen substituents and the reagents employed allow substantial control of the diastereoselectivity during addition of nucleophiles to these aldehydes.²

Engaged in the total synthesis of dolastatin **10**,^{3,4} we needed to prepare (2*R*,3*R*,4*S*)-dolaproine **1** and envisaged the stereochemical control of the three contiguous stereocentres through addition of a (*Z*)-crotylorganoboron compound to Boc-Pro-H **3** via the homoallylic alcohol **2** (Scheme 1).

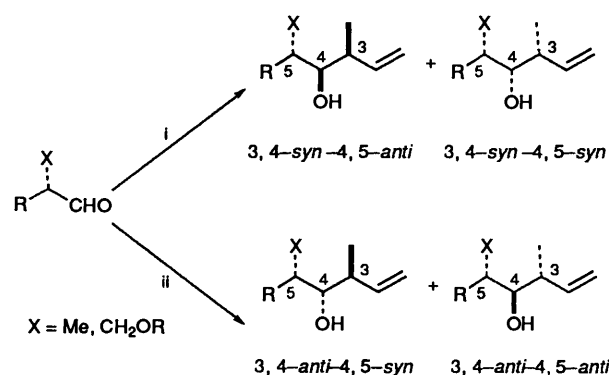


Scheme 1 Retrosynthetic route to (2*R*,3*R*,4*S*)-dolaproine **1**

Indeed, the (*Z*)-crotylboronate (*Z*)-**4**⁵ [eqn. (1)] is known to add regio- and diastereo-selectively to aldehydes, via a presumably six-membered cyclic chair-like transition state,⁶ giving 3,4-*syn* configured homoallylic alcohols since the stereochemical information is transmitted about the newly created C-C bond of the adduct.^{7a} Moreover, in cases where aldehydes bear an α -methyl^{7b} or α -alkoxy^{7c} group (Scheme 2), the (*Z*)-crotylboronate esters furnish preferentially the *anti*-Cram configured stereoisomers, while the (*E*)-crotylboronate esters lead to major Cram products.



Furthermore, addition of a racemic lithio enolate⁸ or an enolborinate⁹ to Boc-Pro-H **3** also yields essentially the *anti*-Cram adduct which corresponds to a more accessible *re* face of this (*S*)-configured aldehyde. It therefore appeared interesting



Scheme 2 Reagents: i, (*Z*)-**4**; ii, (*E*)-**4**

to conjugate both *anti*-Cram effects to obtain the 2,1'-*anti*-1',2'-*syn* linkage present in compound **2**.

We report herein our results on the level of asymmetric induction observed during the addition of achiral (*Z*)-crotylboronate **4** to Boc-Pro-H and other *N*-(*tert*-butoxycarbonyl)amino aldehydes. The double stereodifferentiation through the addition of chiral (*Z*)-crotylorganoboron compounds to Boc-Pro-H is also investigated.

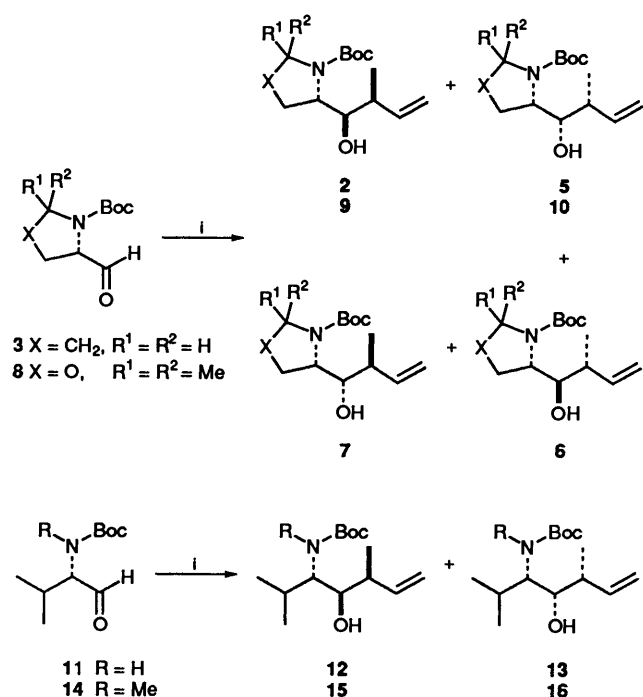
The addition of (*Z*)-**4** was performed with the cyclic aldehydes **3** and **8**¹⁰ and the linear aldehydes **11** and **14** (Scheme 3). Our results show that the reaction proceeds with modest to good yields and the formation of the *anti* diastereoisomer is favoured in all cases (Table 1). This observed diastereoselectivity is especially high for Boc-Pro-H **3** (Table 1, entry 1) and ^{Boc}Val-H **14** (Table 1, entry 5). The slightly lower ratio ^{Me}**13** (Table 1, entry 4) cannot be explained solely by the presence of a less sterically demanding secondary amide since Garner's aldehyde **8** exhibits an equivalent degree of diastereoselectivity (Table 1, entry 3).

In the case of Boc-Pro-H **3**, we isolated the expected adducts **2** and **5** and also compounds **6** and **7** possessing the 1',2'-*anti* linkage‡ in the proportions 84:9:5:2, giving an *anti*-Cram: Cram ratio of 89:11. The assignment of their absolute configurations was recently and unambiguously established in the course of the total synthesis of dolastatin **10**.⁴

The addition of achiral (*E*)-crotylboronate (*E*)-**4**⁵ (Scheme 2) led, interestingly, to a mixture of compounds **2**, **6** and **7** in the proportions 5:69:26 where the *anti*-Cram adducts **2** and **6** predominate (Table 1, entry 2). This is in contrast with previous

‡ Stereochemical purity of (*Z*)-**4** was estimated to be >98% by ¹H NMR spectroscopy. Compounds **6** and **7** should arise from a boat-like rather than from a chair-like transition state.

† Crotyl = but-2-enyl.



Scheme 3 Reagents and conditions: i, 4, THF, room temp.

Table 1 The addition of (*Z*)-4^a to aldehydes 3, 8, 11 and 14

Entry	Aldehyde	Reaction time ^b (t/h)	Yield (%) ^c	Quotient ^d anti/syn
1	3	72	70	89/11 ^f
2	3	60	81	74/26 ^f
3	8	72	46	75/25
4	11	24	78	72/28
5	14	96 ^e	85	86/14

^a Except for entry 2 where (*E*)-4 was used. ^b Reaction performed at room temperature except for entry 5. ^c After chromatographic purification. ^d Refers to *anti*-Cram vs. Cram addition product. ^e Reaction performed at 45 °C. ^f Quotient (2 + 6)/(5 + 7).

Table 2 ¹H NMR data for oxazolidinones 17–22

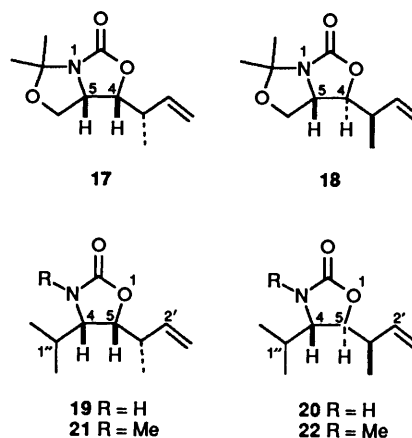
	17	19	21	18	20	22
δ(4-H)	4.35	3.53	3.45	3.97–4.05	3.30	3.24
δ(5-H)	4.21	4.34	4.15	3.54–3.59	4.05	3.97
J _{4,5} (Hz)	7.8	7.0	6.9	n.d. ^a	3.8	3.3

^a J_{4,5} could not be determined since 4-H and 6-H signals overlap.

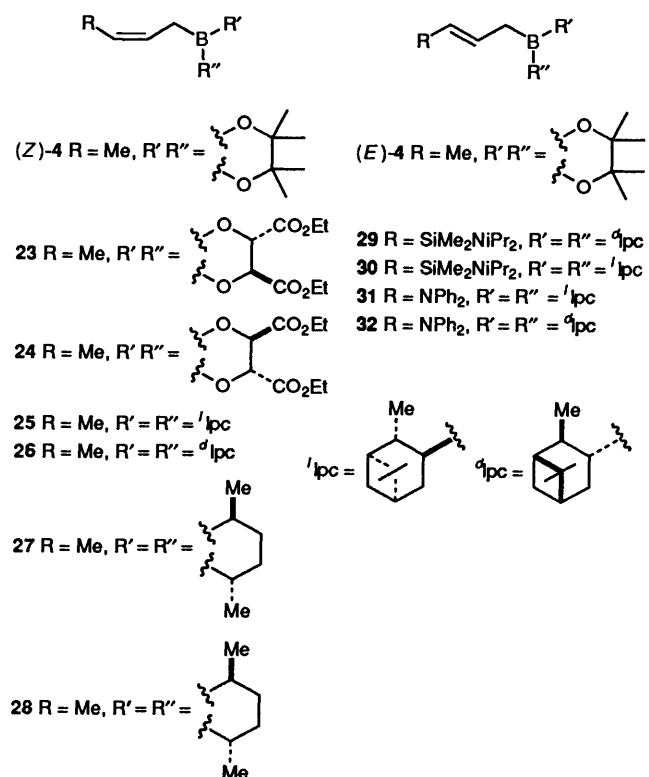
results^{7b} showing a high Cram selectivity during the addition of boronate (*E*)-4 to α-methyl-branched aldehydes.

In the case of aldehydes 8, 11 and 14, we observed that addition of compound (*Z*)-4 led to the formation of *anti*-Cram adducts 9, 12, 15 and Cram adducts 10, 13, 16. Each diastereoisomeric pair was successfully separated except for compounds 12 and 13. Their absolute configurations were assigned after cyclisation of each adduct into the corresponding oxazolidinones 17–22 under basic conditions and by assuming that (*Z*)-crotylboration is 1',2'-*syn* selective.⁶ In fact, it was not possible to detect any trace of diastereoisomeric compound possessing the 1',2'-*anti* linkage in the adducts 9, 10, 12, 13, 15 and 16 from a study of the ¹H NMR spectra of the corresponding oxazolidinones 17–22. By cyclisation, it was possible to distinguish between a 4,5-*trans*-disubstituted

oxazolidinone and its 4,5-*cis*-analogue by using ¹H NMR spectroscopy.^{11,12} The 4-H and 5-H protons resonate systematically at higher field (Table 2) for the *cis*-oxazolidinones 17, 19 and 21 than for the *trans*-oxazolidinones 18, 20 and 22. Higher coupling constants J_{4,5} are also observed for the *cis*-oxazolidinones.



The high diastereofacial selectivity of Boc-Pro-H 3 (8.1:1) towards achiral (*Z*)-4 prompted us to study the addition of this aldehyde to chiral (*Z*)-crotylorganoboron compounds. A single previous example¹³ of double stereodifferentiation was described concerning the addition of chiral (*E*)-crotylboranes 29 and 30 to an α-amino aldehyde, namely compound 8, and



subsequent oxidative desilylation of the adducts to give the homoallylic alcohols 33 and 34. Very good diastereoselectivity was observed for the matched pair¹⁴ (Table 3, entry 1) but a 67:33 ratio for the mismatched pair was observed (Table 3, entry 2). To our knowledge, this represents the first case where both enantiomers of a chiral crotylorganoboron derivative have the *same* diastereoselection with respect to the addition to

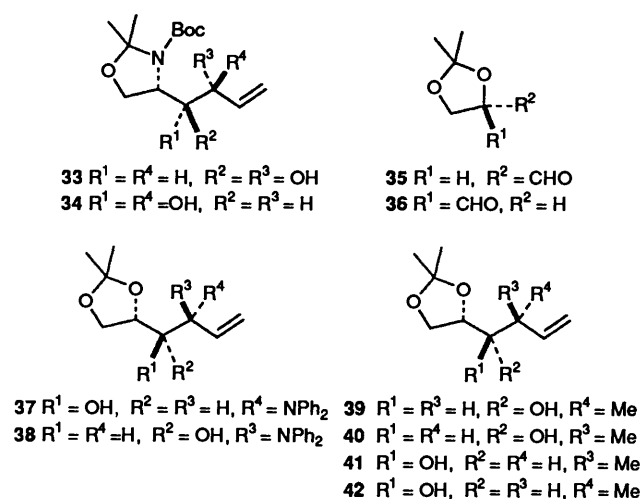


Table 3 The addition of chiral crotylorganoboron compounds to aldehydes **3**, **8**, **35** and **36**

Entry	Crotylboron compound	Aldehyde	Yield (%)	Reaction time (t/h)	Ratio ^a <i>anti</i> : <i>syn</i>
1	29	8	57 ^b	3	98:2 ^c
2	30	8	45 ^b	3	67:33 ^c
3	23	3	68 ^d	14	96:4 ^e
4	24	3	72 ^d	14	87:13 ^e
5	25	3	50 ^b	2	99:1 ^e
6	26	3	49 ^b	2	80:20 ^e
7	31	35	28 ^b	3	100:0 ^f
8	32	35	29 ^b	3	21:79 ^f
9	27	36	66 ^b	4	97:3 ^g
10	28	36	65 ^b	4	16:84 ^g

^a Refers to *anti*-Cram *vs.* Cram addition product. ^b Reaction performed at -78°C . ^c Ref. 13. ^d The reagent was added at -50°C before the mixture was stirred at room temperature. ^e Ratio (**2** + **6**): (**5** + **7**) (see Experimental section). ^f Ref. 17. ^g Ref. 18.

an α -chiral amino aldehyde, suggesting the presence of substrate-controlled diastereoselectivity during these additions, instead of the expected diastereodifferentiation with these chiral reagents. Conversely, the reaction of chiral (*Z*)- or (*E*)-crotylboron compounds with α -alkoxy- or α -methyl-branched aldehydes led to inversion of the sense of the addition Cram *vs.* *anti*-Cram.^{7c}

We first selected the chiral (*Z*)-crotylboronates **23** and **24** developed by Roush¹⁵ which show great potency in terms of double asymmetric induction and have the advantage of being derived from the same cyclic precursor. In our case, the matched pair exhibited an expected higher proportion (96:4) of *anti*-Cram adducts **2** and **6** (Table 3, entry 3) than with the achiral crotylboronate (*Z*)-**4** (Table 1, entry 1). The diastereoselectivity dropped to 87:13 when compound **24** was used (Table 3, entry 4) but the *anti*-Cram stereoisomers were favoured as in Barrett's work cited above.¹³

Among the crotylorganoboron compounds, those developed by Brown¹⁶ are considered as the most powerful stereodirecting reagents. Effectively, the addition of (ⁱIpc)₂B-(*Z*)-crotylborane* **25** to aldehyde **3** produced quasi-exclusively compound **2** (Table 3, entry 5) while a 80:20 ratio of products **2**:**5** was observed when using (^dIpc)₂B-(*Z*)-crotylborane **26** (Table 3, entry 6), still favouring the *anti*-Cram adducts, at variance with the previously related behaviour of this reagent.¹⁶

* Abbreviations used: (ⁱIpc), isopinocampheyl derived from (–)- α -pinene; (^dIpc), isopinocampheyl derived from (+)- α -pinene (ref. 16).

This set of results, including the high diastereofacial selectivity of Boc-Pro-H **3** towards achiral boronate (*Z*)-**4**, emphasises an unusual behaviour of this aldehyde when adding to the (*Z*)-crotylorganoboron derivatives, since these reactions proceed under substrate control. It is of interest to compare these observations with the diastereoselectivities observed for L-glyceraldehyde acetonide **35**, where the α -substituent is an oxygen instead of a nitrogen atom. A recent example involves the addition of (*E*)-crotylboranes **31** and **32**¹⁷ to aldehyde **35** (Table 3, entries 7 and 8), which shows complete diastereoselectivity for the matched pair and a predominantly Cram product for the mismatched pair (**37**:**38** = 21:79). This trend was confirmed when using Masamune's reagents¹⁸ **27** and **28**, starting from D-glyceraldehyde acetonide **36**. The former gives a high ratio of *anti*-Cram stereoisomers **39** and **40** to Cram adducts **41** and **42** (Table 3, entry 9) while a predominant proportion of Cram adducts (Table 3, entry 10) was obtained by using the borane **28**.¹⁸ It should be noted that the (*Z*)-crotylboronate esters gave rise to a higher proportion of *anti*-Cram adducts when added to the cyclic aldehyde **36** than they did when added to α -alkoxy aldehydes.^{7c} Under the same reaction conditions, these latter compounds behave more diastereoselectively than did α -methyl-branched aldehydes, highlighting the strong influence of an α -oxygen atom on the π -facial diastereoselectivity in such additions.

Although the Felkin–Ahn model is recognised as the most appropriate model to account for high *anti*-Cram diastereoselectivities in non-chelation-controlled reactions,¹⁹ several effects participate in the stabilisation of the lowest energetic transition state in α -methoxy- and α -(dimethylamino)propanal, as recently shown by Reetz.²⁰ The influence of a nitrogen *vs.* an oxygen atom should be cautiously evaluated since electronic effects cannot alone account for such discrepancies in the observed diastereoselectivities. Steric and coulombic interactions and conformational energies as well may play a non-negligible role in this π -facial diastereoselectivity. Investigations are currently under way to gain a better understanding of these results.

In conclusion, we show that (ⁱIpc)₂B-(*Z*)-crotylborane **25** is a very efficient reagent for the synthesis of the homoallylic alcohol **2**, precursor of the doloproline residue where the diastereofacial selectivities of both substrate and reagent match. The *N*-(*tert*-butoxycarbonyl)amino aldehydes, especially Boc-Pro-H **3**, present such diastereofacial selectivity that the reaction proceeds under substrate control. Further studies are necessary to delineate how the nitrogen bearing substituent(s) acts upon the diastereoselectivity observed on addition of these crotylboron derivatives to α -amino aldehydes.

Experimental

360 MHz ¹H NMR spectra were recorded in CDCl₃ on a Bruker WM-360 spectrometer. δ_{H} -Values are given in ppm, and *J* values are given in Hz. Mass spectra were obtained in the FAB+ mode from the Department of Physical Measurements of the University of Montpellier II. Elemental analyses were carried out in the Service Central de Microanalyse at the Ecole Nationale Supérieure de Chimie de Montpellier. Column chromatography was performed using silica gel manufactured by Merck and Co., Kiesel 60, 230–400 mesh. Analytical TLC was conducted on silica gel 60F₂₅₄ aluminium sheets (0.2 μm thick) manufactured by Merck and Co. Optical rotations were run at 20 $^{\circ}\text{C}$ on a Schmidt and Haensch Polartronic D polarimeter in a 10 cm cell, and are given in units of 10⁻¹ deg cm² g⁻¹.

Anhydrous tetrahydrofuran (THF), purchased from Janssen, was distilled over lithium aluminium hydride prior to use.

Aldehydes **3**, **8**, **11** and **14** were prepared by reduction of

their corresponding *N,O*-dimethylamides²¹ and used directly without further purification. These latter compounds were synthesized from the corresponding *N*-Boc-*L*-amino acids.²¹ Full experimental details of the (*Z*)-crotylboration of Boc-Pro-H 3 with boronate (*Z*)-4 are given elsewhere.⁴

O-Benzyl-*N*-(*tert*-butoxycarbonyl)-*L*-serine *N'*-Methoxy-*N'*-methylamide.—To a stirred solution of *O*-benzyl-*N*-(*tert*-butoxycarbonyl)-*L*-serine (14.75 g, 50 mmol) in dichloromethane (75 cm³) were added triethylamine (24.6 cm³, 175 mmol) and (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP; 17.41 g, 50 mmol). After 5 min, *N,O*-dimethylhydroxylamine hydrochloride (5.36 g, 55 mmol) was added to the mixture. After 1 h the mixture was diluted with dichloromethane and washed successively with aq. HCl (3 mol dm⁻³), saturated aq. sodium hydrogen carbonate and brine. The organic phase was dried and concentrated to afford the *title compound* (14.9 g, 88%) as a crystalline residue, m.p. 84 °C (from diethyl ether–pentane); *R*_f 0.40 [AcOEt–pentane (3:7; v/v)]; [α]_D –10 (c 1, MeOH) (Found: C, 60.5; H, 7.9; N, 8.4. C₁₇H₂₆N₂O₅ requires C, 60.3; H, 7.7; N, 8.3%); δ _H 1.42 (9 H, s, Bu'), 3.18 (3 H, s, NMe), 3.65–3.69 (2 H, m, CH₂OCH₂Ph), 3.70 (3 H, s, OMe), 4.48 (1 H, d, *J* 12.2, OCH₂Ph), 4.55 (1 H, d, *J* 12.2, OCH₂Ph), 4.87 (1 H, m, NHCH), 5.40 (1 H, d, *J* 8.8, NH) and 7.23–7.34 (5 H, m, Ph); *m/z* 338 (MH⁺, 54%), 283 (67), 239 (100), 237 (14), 175 (17), 150 (24), 91 (95) and 57 (32).

N-(*tert*-Butoxycarbonyl)-*L*-serine *N'*-Methoxy-*N'*-methylamide.—A solution of *O*-benzyl-*N*-(*tert*-butoxycarbonyl)-*L*-serine *N'*-methoxy-*N'*-methylamide (13.8 g, 41 mmol) and palladium on charcoal (2.76 g, 20% w/w) in methanol (185 cm³) was hydrogenated at atmospheric pressure and room temp. for 20 h. After filtration on a Celite pad, the mixture was concentrated to give the *title compound* (7.33 g, 73%) as a crystalline residue, m.p. 116.5 °C (from acetone) (lit.,²² 116–117 °C); *R*_f 0.27 [AcOEt–pentane (2:3; v/v)]; [α]_D +1 (c 1, CHCl₃) [lit.,²² +1.1 (c 1, CHCl₃)]; δ _H 1.37 (9 H, s, Bu'), 3.10 (3 H, s, NMe), 3.47 (1 H, ddd, *J* 10.9, 6.5 and 6.1, CH^aH^bOH), 3.55 (1 H, ddd, *J* 10.9, 5.3 and 4.9, CH^aH^bOH), 3.71 (3 H, s, OMe), 4.50 (1 H, m, NHCH), 4.78 (1 H, dd, *J* 6.1 and 5.3, OH) and 6.71 (1 H, d, *J* 8.1, NH).

N-(*tert*-Butoxycarbonyl)-*N*-methyl-*L*-valine *N'*-Methoxy-*N'*-methylamide.—The *title compound* was prepared as above from *N*-(*tert*-butoxycarbonyl)-*N*-methyl-*L*-valine²³ (5 g, 21.6 mmol). After flash chromatography on silica gel with ethyl acetate–pentane (1:4; v/v), the *title compound* (3.65 g, 62%) was obtained as an oil; *R*_f 0.58 [AcOEt–pentane (2:8; v/v)]; [α]_D –121 (c 1.01, MeOH) (Found: C, 59.2; H, 9.4; N, 10.5. C₁₂H₂₆N₂O₄ requires C, 59.0; H, 9.3; N, 10.8%); δ _H 2 conformers (2:1) 0.83 (4 H, d, *J* 6.8, Me of Pr^a), 0.85 (2 H, d, *J* 6.8, Me of Pr^b), 1.41 (6 H, s, Bu'), 1.44 (3 H, s, Bu'), 2.22 (1 H, m, CHMe₂), 2.75 (1 H, s, NMe), 2.78 (2 H, s, NMe), 3.15 (3 H, s, NMe), 3.63 (1 H, s, OMe), 3.67 (2 H, s, OMe), 4.65 (0.33 H, d, *J* 6.3, NMeCH) and 4.95 (0.66 H, d, *J* 6.3, NMeCH); *m/z* 275 (MH⁺, 72%), 219 (65), 214 (9), 186 (12), 175 (21), 130 (68), 86 (65), 62 (58), 57 (100) and 43 (60).

(*Z*)-Crotylboration of Aldehyde 8.—To a solution of aldehyde 8¹⁰ (0.74 g, 3.23 mmol) in THF (5 cm³) was added at room temp. the (*Z*)-crotylboronate 4⁵ (0.745 g, 4.09 mmol). After being stirred for 72 h, the mixture was concentrated, and purified by flash chromatography on silica gel with ethyl acetate–pentane (1:9; v/v) to afford the homoallyl alcohols 9 and 10 as oily products in the ratio 75:25 (0.41 g, 45% combined yield).

Compound 9: *R*_f 0.35 [AcOEt–pentane (1:9; v/v)] (Found: C, 66.7; H, 9.4; N, 4.7. C₁₅H₂₇NO₄ requires C, 66.9; H, 9.5; N, 4.5%); δ _H 1.12 (3 H, d, *J* 6.7, 2'-Me), 1.47 (9 H, s, Bu'), 1.48 (3 H, s, 2-Me), 1.59 (3 H, s, 2-Me), 2.15–2.23 (1 H, m, 2'-H), 3.79–3.85 (1 H, m, 1'-H), 3.88 (1 H, dd, *J* 9.1 and 6.8, 5-H), 4.02–4.12 (2 H, m, 4- and 5-H), 5.00 (1 H, dd, *J* 10.4 and 1.6, 4'-H), 5.02 (1 H, dd, *J* 18.2 and 1.7, 4'-H) and 5.69–5.76 (1 H, m, 3'-H); *m/z* 286 (MH⁺, 6%), 230 (21), 212 (6), 186 (16), 172 (27), 154 (25), 136 (22), 109 (32), 95 (53), 81 (54), 69 (73), 57 (100), 55 (87), 43 (48) and 41 (38).

Compound 10: *R*_f 0.65 [AcOEt–pentane (1:9; v/v)]; δ _H 1.05 (3 H, d, *J* 6.8, 2'-Me), 1.48 (9 H, s, Bu'), 1.49 (3 H, s, 2-Me), 1.57 (3 H, s, 2-Me), 2.19–2.24 (1 H, m, 2'-H), 3.58 (1 H, dd, *J* 9.6 and 3.2, 1'-H), 3.76 (1 H, dd, *J* 9.3 and 1.1, 5-H), 3.90 (1 H, dd, *J* 9.3 and 5.7, 5-H), 4.01–4.05 (1 H, m, 4-H), 5.02 (1 H, dd, *J* 10.3 and 1.3, 4'-H), 5.02 (1 H, dd, *J* 17.2 and 1.5, 4'-H) and 5.87 (1 H, ddd, *J* 17.2, 10.3 and 7.5, 3'-H); *m/z* 286 (MH⁺, 33%), 230 (72), 186 (18), 172 (70), 154 (41), 136 (32), 109 (20), 95 (33), 81 (35), 69 (47), 57 (100), 55 (58), 43 (40) and 41 (32).

(*Z*)-Crotylboration of Aldehyde 11.—The same procedure as above was applied to Boc-Val-H 11 (2.03 g, 10.1 mmol) and the (*Z*)-crotylboronate 4 (2.72 g, 14.9 mmol) in THF (25 cm³) at room temp. for 24 h. Purification by flash chromatography on silica gel with ethyl acetate–pentane (1:9; v/v) afforded an inseparable mixture of compounds 12 and 13 (2.02 g, 78% combined yield) whose ratio (72:28) was estimated from the following ¹H NMR data.

Compound 12: oil; *R*_f 0.31 [AcOEt–pentane (1:9; v/v)]; δ _H 0.80 (3 H, d, *J* 6.8, 6-Me), 0.92 (3 H, d, *J* 6.8, 6-Me), 1.01 (3 H, d, *J* 6.3, 3-Me), 1.38 (9 H, s, Bu'), 2.15 (1 H, m, 6-H), 2.37 (1 H, m, 3-H), 3.37–3.45 (1 H, m, 4-H), 3.56 (1 H, ddd, *J* 10.0, 8.1 and 3.4, 5-H), 4.48 (1 H, d, *J* 10.0, NH), 4.97–5.10 (2 H, m, 1-H₂) and 5.79 (1 H, ddd, *J* 17.6, 10.7 and 7.2, 2-H).

Compound 13: oil; *R*_f 0.31 [AcOEt–pentane (1:9; v/v)]; δ _H 0.80 (3 H, d, *J* 6.8, 6-Me), 0.91 (3 H, d, *J* 6.5, 6-Me), 1.04 (3 H, d, *J* 6.3, 3-Me), 1.38 (9 H, s, Bu'), 1.82 (1 H, m, 6-H), 2.25 (1 H, m, 3-H), 3.29 (1 H, ddd, *J* 9.4, 8.1 and 1.9, 5-H), 3.37–3.45 (1 H, m, 4-H), 4.79 (1 H, d, *J* 9.4, NH), 4.97–5.10 (2 H, m 1-H₂) and 5.67 (1 H, ddd, *J* 17.6, 10.2 and 8.5, 2-H).

(*Z*)-Crotylboration of Aldehyde 14.—To ^{Boc}Me>Val-H 14 (0.71 g, 3.3 mmol), obtained after reduction of *N*-(*tert*-butoxycarbonyl)-*N*-methyl-*L*-valine *N'*-methoxy-*N'*-methylamide and used without further purification, was added a solution of the (*Z*)-crotylboronate 4 (0.94 g, 5.16 mmol) in THF (10 cm³); the mixture was stirred at 45 °C for 96 h. Purification by flash chromatography on silica gel with ethyl acetate–pentane (1:19; v/v) afforded the homoallyl alcohols 15 and 16 as oily products in the ratio 86:14 (0.70 g, 79% combined yield).

Compound 15: oil; *R*_f 0.36 [AcOEt–pentane (1:9; v/v)]; δ _H 2 conformers (1:1) 0.89 (3 H, d, *J* 6.7, 6-Me), 0.92 (3 H, d, *J* 7.0, 6-Me), 1.06 (3 H, d, *J* 6.7, 3-Me), 1.43 (4.5 H, s, Bu'), 1.45 (4.5 H, s, Bu'), 2.15 (0.5 H, m, 6-H), 2.37–2.48 (1.5 H, m, 3- and 6-H), 2.72 (1.5 H, s, NMe), 2.76 (1.5 H, s, NMe), 3.62 (1 H, m, 5-H), 3.76 (0.5 H, m, 4-H), 3.86 (0.5 H, m, 4-H), 5.04–5.13 (2 H, m, 1-H₂) and 5.59–5.93 (1 H, m, 2-H); *m/z* 272 (MH⁺, 31%), 216 (100), 198 (26), 186 (18), 172 (24), 154 (12), 130 (73), 123 (13), 95 (11), 86 (31), 73 (52), 57 (54), 55 (23), 43 (16) and 41 (15).

Compound 16: oil; *R*_f 0.46 [AcOEt–pentane (1:9; v/v)]; δ _H 0.88 (3 H, d, *J* 6.5, 6-Me), 0.97 (3 H, d, *J* 6.3, 6-Me), 1.13 (3 H, d, *J* 6.7, 3-Me), 1.44 (9 H, s, Bu'), 2.16–2.27 (1 H, m, 6-H), 2.52–2.54 (1 H, m, 3-H), 2.83 (3 H, s, NMe), 3.43–3.49 (2 H, m, 4- and 5-H), 4.97–5.04 (2 H, m, 1-H₂) and 5.60 (1 H, ddd, *J* 18.4, 10.0 and 8.5, 2-H); *m/z* 272 (MH⁺, 41%), 216 (100), 186 (22), 172 (21), 154 (14), 130 (58), 123 (15), 95 (9), 86 (28), 73 (58), 57 (72), 55 (45), 43 (26) and 41 (21).

General Procedure for the Cyclisation of Compounds 9, 12, 13, 15 and 16.—To a solution of compound **9** (0.143 g, 0.5 mmol) in THF (2 cm³) at -5 °C under argon was added NaH (0.040 g, 1 mmol, as a 60% dispersion in oil). The mixture was stirred overnight at room temp., then was hydrolysed with aq. 5% KHSO₄. After dilution with diethyl ether, the organic phase was washed successively with saturated aq. sodium hydrogen carbonate and brine, dried, and concentrated. The cyclised product **17** was purified by column chromatography on silica gel with ethyl acetate–pentane.

Compound 17: oil; *R_f* 0.67 [AcOEt–pentane (1:4; v/v)]; [α]_D -2 (*c* 0.68, MeOH) (Found: C, 62.4; H, 8.0; N, 6.5. C₁₁H₁₇NO₃ requires C, 62.5; H, 8.1; N, 6.6%); δ_H 1.18 (3 H, d, *J* 6.5, 1'-Me), 1.41 (3 H, s, 8-Me), 1.71 (3 H, s, 8-Me), 2.43–2.46 (1 H, m, 1'-H), 3.66 (1 H, dd, *J* 9.4 and 8.5, 6-H), 3.91 (1 H, dd, *J* 8.5 and 6.0, 6-H), 4.21 (1 H, ddd, *J* 9.4, 7.8 and 6.0, 5-H), 4.35 (1 H, dd, *J* 10.5 and 7.8, 4-H), 5.11 (1 H, d, *J* 18.0, 3'-H), 5.13 (1 H, d, *J* 9.8, 3'-H) and 5.61 (1 H, ddd, *J* 18.0, 9.8 and 8.3, 2'-H); *m/z* 212 (MH⁺, 100%), 210 (12), 172 (17), 154 (42), 136 (38), 115 (20), 97 (23), 91 (37), 77 (65), 55 (88) and 41 (76).

Compound 18: oil; *R_f* 0.61 [AcOEt–pentane (1:4; v/v)]; [α]_D -4 (*c* 0.24, MeOH) (Found: C, 62.6; H, 8.1; N, 6.5%); δ_H 1.13 (3 H, d, *J* 6.7, 1'-Me), 1.41 (3 H, s, 8-Me), 1.69 (3 H, s, 8-Me), 2.49–2.55 (1 H, m, 1'-H), 3.54–3.59 (1 H, m, 5-H), 3.97–4.05 (3 H, m, 4-H and 6-H₂), 5.12–5.20 (2 H, m, 3'-H₂) and 5.62 (1 H, ddd, *J* 17.7, 10.1 and 7.6, 2'-H); *m/z* 212 (MH⁺, 100%), 210 (14), 172 (20), 154 (40), 136 (48), 115 (16), 97 (19), 91 (35), 77 (56), 55 (81) and 41 (57).

Compound 19: oil; *R_f* 0.18 [AcOEt–pentane (1:4; v/v)]; [α]_D -35 (*c* 0.32, MeOH) (Found: C, 65.5; H, 9.3; N, 7.7. C₁₀H₁₇NO₂ requires C, 65.5; H, 9.4; N, 7.6%); δ_H 0.89 (3 H, d, *J* 6.8, 1''-Me), 0.96 (3 H, d, *J* 6.8, 1''-Me), 1.19 (3 H, d, *J* 6.6, 1'-Me), 2.06 (1 H, hept-d, *J* 6.8 and 3.3, 1''-H), 2.66 (1 H, m, 1'-H), 3.53 (1 H, dd, *J* 7.0 and 3.3, 4-H), 4.34 (1 H, dd, *J* 9.6 and 7.0, 5-H), 5.11 (1 H, dd, *J* 10.5 and 0.7, 3'-H), 5.14 (1 H, dd, *J* 16.8 and 1.1, 3'-H), 5.58 (1 H, br s, NH) and 5.65 (1 H, ddd, *J* 16.8, 10.5 and 6.6, 2'-H); *m/z* 184 (MH⁺, 100%), 140 (3), 123 (10), 116 (30), 93 (21), 91 (5), 75 (7), 57 (7), 55 (6) and 41 (3).

Compound 20: oil; *R_f* 0.32 [AcOEt–pentane (1:4; v/v)]; [α]_D -23 (*c* 0.41, MeOH) (Found: C, 65.7; H, 9.4; N, 7.8%); δ_H 0.87 (3 H, d, *J* 6.7, 1''-Me), 0.87 (3 H, d, *J* 7.1, 1''-Me), 1.07 (3 H, d, *J* 6.8, 1'-Me), 1.63 (1 H, m, 1'-H), 2.38 (1 H, m, 1'-H), 3.30 (1 H, dd, *J* 6.1 and 3.8, 4-H), 4.05 (1 H, dd, *J* 6.6 and 3.8, 5-H), 5.08 (1 H, dd, *J* 10.4 and 1.0, 3'-H), 5.12 (1 H, dd, *J* 17.2 and 1.0, 3'-H), 5.64 (1 H, ddd, *J* 17.2, 10.4 and 8.0, 2'-H) and 7.05 (1 H, d, *J* 7.5, NH); *m/z* 184 (MH⁺, 100%), 182 (65), 154 (6), 123 (18), 116 (48), 95 (12), 81 (15), 69 (15), 57 (15), 55 (27), 43 (16) and 41 (13).

Compound 21: oil; *R_f* 0.34 [AcOEt–pentane (1:4; v/v)]; [α]_D -28 (*c* 0.65, MeOH) (Found: C, 66.6; H, 9.6; N, 6.9. C₁₁H₁₉NO₂ requires C, 67.0; H, 9.7; N, 7.1%); δ_H 0.94 (3 H, d, *J* 6.8, 1''-Me), 1.06 (3 H, d, *J* 7.3, 1''-Me), 1.18 (3 H, d, *J* 6.6, 1'-Me), 2.14 (1 H, m, 1''-H), 2.61 (1 H, m, 1'-H), 2.98 (3 H, s, NMe), 3.45 (1 H, d, *J* 6.9, 4-H), 4.15 (1 H, dd, *J* 11.0 and 6.9, 5-H), 5.11 (1 H, d, *J* 10.4, 3'-H), 5.14 (1 H, d, *J* 17.5, 3'-H) and 5.64 (1 H, ddd, *J* 17.5, 10.4 and 7.5, 2'-H); *m/z* 212 (MH⁺, 100%), 210 (22), 172 (15), 154 (38), 136 (34), 115 (23), 91 (27), 77 (45), 63 (27), 55 (74) and 51 (53).

Compound 22: oil; *R_f* 0.45 [AcOEt–pentane (1:4; v/v)]; [α]_D -20 (*c* 0.21, MeOH) (Found: C, 66.7; H, 9.8; N, 7.0%); δ_H 0.85 (3 H, d, *J* 6.9, 1''-Me), 0.87 (3 H, d, *J* 6.9, 1''-Me), 1.06 (3 H, d, *J* 6.6, 1'-Me), 1.97 (1 H, hept-d, *J* 6.6 and 3.3, 1''-H), 2.36 (1 H, m, 1'-H), 2.82 (3 H, s, NMe), 3.24 (1 H, dd, *J* 6.4, and 3.3, 4-H), 3.97 (1 H, dd, *J* 6.4 and 3.3, 5-H), 5.12 (1 H, d, *J* 9.9, 3'-H), 5.13 (1 H, d, *J* 17.7, 3'-H) and 5.64 (1 H, ddd, *J* 17.7, 9.9 and 7.9, 2'-H); *m/z* 212 (MH⁺, 100%), 210 (12), 172 (17), 154

(42), 136 (38), 115 (20), 91 (37), 77 (65), 63 (36), 55 (88) and 41 (76).

(Z)-Crotylboration of Aldehyde 3 with Compound 23.—To a solution of Boc-Pro-H **3**²³ (0.398 g, 2 mmol) in dry THF (5 cm³) containing 4 Å molecular sieves (0.1 g) was added at -50 °C the (Z)-crotylboronate **23**¹⁵ (2.2 cm³ of a 1 mol dm⁻³ solution in THF, 2.2 mmol). After reaching room temp., the mixture was stirred for 14 h, filtered through a short pad of silica gel, and concentrated. The residue was then purified by flash chromatography on silica gel with ethyl acetate–cyclohexane (1:4; v/v) to afford, by order of elution, compounds **5**, **6** and **2**⁴ in the proportions 4:4:92 (68% combined yield).

(Z)-Crotylboration of Aldehyde 3 with Compound 24.—By the same procedure as above, compounds **5**, **6** and **2**⁴ were obtained in the proportions 13:5:82 (72% combined yield).

(Z)-Crotylboration of Aldehyde 3 with Compound 25.—Brown's procedure¹⁶ was applied to prepare (1³C)₂B-(Z)-crotylborane **25** starting from *B*-methoxydiisopinocampheylborane (10.76 g, 34 mmol) derived from (-)-α-pinene. To a cooled solution of compound **25** in THF (30 cm³) at -78 °C was added Boc-Pro-H **3** (6.8 g, 34.2 mmol) over a 1 h period. The reaction mixture was stirred for 2 h at -78 °C, quenched with 30% H₂O₂ (7.5 cm³) and aq. NaOH (3 mol dm⁻³, 18 cm³), then was slowly warmed to room temp. and finally heated under reflux for 1 h. The mixture was cooled to room temp. and diluted with diethyl ether. The organic phase was washed successively with water and brine, dried, and concentrated to give, after chromatographic purification on silica gel with ethyl acetate–hexane (1:4; v/v), the compound **2** (4.36 g, 50%) as a single diastereoisomer.

(Z)-Crotylboration of Aldehyde 3 with Compound 26.—By the same procedure as for compound **25**, compounds **5** and **2** were obtained in the ratio 20:80 (49% combined yield) after chromatographic purification on silica gel with ethyl acetate–hexane (1:4; v/v).

References

- P. A. Grieco and E. D. Moher, *Tetrahedron Lett.*, 1993, **34**, 5567; M. T. Reetz, J. Kanand, N. Griebenow and K. Harms, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 1626; M. Franzotti, A. Mann and M. Taddei, *Tetrahedron Lett.*, 1991, **32**, 6783; J. Jurczak and A. Golebiowski, *Chem. Rev.*, 1989, **89**, 149; F. Bigi, G. Casnati, G. Sartori, G. Araldi and G. Bocelli, *Tetrahedron Lett.*, 1989, **30**, 1121.
- W. R. Li, S. Y. Han and M. Joullie, *Heterocycles*, 1993, **36**, 359; T. Yokomatsu, Y. Yuasa and S. Shibuya, *Heterocycles*, 1992, **33**, 1051; J. D. Armstrong, III, F. W. Hartner, Jr., A. E. DeCamp, R. P. Volante and I. Shinkai, *Tetrahedron Lett.*, 1992, **33**, 6599; A. Hafner, R. O. Duthaler, R. Marti, G. Rihs, P. Rothe-Streit and F. Schwarzenbach, *J. Am. Chem. Soc.*, 1992, **114**, 2321; R. S. Coleman and A. J. Carpenter, *Tetrahedron Lett.*, 1992, **33**, 1697; M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1531; K. Hayashi, Y. Hamada and T. Shioiri, *Tetrahedron Lett.*, 1991, **32**, 7287; J. V. N. Vara Prasad and D. H. Rich, *Tetrahedron Lett.*, 1990, **31**, 1803.
- G. R. Pettit, Y. Kamano, C. L. Herald, A. A. Tuinman, F. E. Boettner, H. Kizu, J. M. Schmidt, L. Baczynskyj, K. B. Tomer and R. J. Bontems, *J. Am. Chem. Soc.*, 1987, **109**, 6883.
- F. Roux, I. Maugras, J. Poncet, G. Niel and P. Jouin, *Tetrahedron*, in the press.
- R. W. Hoffmann and H. J. Zeiss, *J. Org. Chem.*, 1981, **46**, 1309.
- R. W. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, 1982, **21**, 555.
- (a) For a recent review on allylic metals, see: Y. Yamamoto and N. Asao, *Chem. Rev.*, 1993, **93**, 2207; (b) R. W. Hoffmann and U. Weidmann, *Chem. Ber.*, 1985, **118**, 3966; (c) W. R. Roush, M. A. Adam, A. E. Walts and D. J. Harris, *J. Am. Chem. Soc.*, 1986, **108**, 3422.
- G. J. Hanson, J. S. Baran and T. Lindberg, *Tetrahedron Lett.*, 1986, **27**, 3577.
- K. Tomioka, M. Kanai and K. Koga, *Tetrahedron Lett.*, 1991, **32**, 2395.

- 10 P. Garner and J. M. Park, *J. Org. Chem.*, 1987, **52**, 2361.
- 11 T. Ibuka, H. Habashita, A. Otaka and N. Fujii, *J. Org. Chem.*, 1991, **56**, 4370.
- 12 M. N. Dufour, P. Jouin, J. Poncet, A. Pantaloni and B. Castro, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1895.
- 13 A. G. M. Barrett and J. W. Malecha, *J. Org. Chem.*, 1991, **56**, 5243.
- 14 S. Masamune, W. Choy, J. S. Petersen and L. R. Sita, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 1.
- 15 W. R. Roush, A. D. Palkowitz and K. Ando, *J. Am. Chem. Soc.*, 1990, **112**, 6348.
- 16 H. C. Brown, K. S. Bhat and R. S. Randad, *J. Org. Chem.*, 1989, **54**, 1570.
- 17 A. G. M. Barrett and M. A. Seefeld, (a) *Tetrahedron*, 1993, **49**, 7857; (b) *J. Chem. Soc., Chem. Commun.*, 1993, 339.
- 18 J. Garcia, B. M. Kim and S. Masamune, *J. Org. Chem.*, 1987, **52**, 4831.
- 19 M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 556.
- 20 (a) G. Frenking, K. F. Köhler and M. T. Reetz, *Tetrahedron*, 1993, **49**, 3971; (b) *Tetrahedron*, 1993, **49**, 3983.
- 21 J. A. Fehrentz and B. Castro, *Synthesis*, 1983, 676.
- 22 G. Bold, T. Allmendinger, P. Herold, L. Moesch, H. P. Schär and R. O. Duthaler, *Helv. Chim. Acta*, 1992, **75**, 865.
- 23 S. T. Cheung and N. L. Benoiton, *Can. J. Chem.*, 1977, **55**, 906.

Paper 4/00202D

Received 13th January 1994

Accepted 9th February 1994