Ephedrine-Derived Imidazolidin-2-ones. Broad Utility Chiral Auxiliaries in Asymmetric Synthesis

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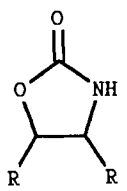
The scope of the readily available (4*R*,5*S*)-1,5-dimethyl-4-phenylimidazolidin-2-one (**4**) and its 4-cyclohexyl analogue **6** as practical, efficient chiral auxiliaries has been demonstrated. The enolate chemistry of their *N*-acyl derivatives exhibits features which recommend their use in asymmetric synthesis. The stereoselective boron-mediated aldol as well as alkylation and acylation results are presented. The steric control benefit derived by conversion of phenyl to cyclohexyl is highlighted.

The current importance of stereocontrol in the construction of acyclic systems has led to the appearance of much elegant chemistry[1]. Noteworthy diastereoselective approaches are those of the Evans[2] and Oppolzer[3] groups, based on their exploitation of oxazolidin-2-ones **1** and camphor-derived chiral auxiliaries **2**, **3**, respectively[4]. Their main disadvantage, i.e. the number of preparative steps, prompted us to investigate the application of the less well studied analogous imidazolidin-2-one system[5]. Its potential as a chiral auxiliary has been exploited with respect to homoaldol condensation[6a], alkylation[6b], Michael addition[6g,h], and Diels-Alder reactions[6i] but neither hydroxyalkylations (with aldehydes) nor acylations (with acyl halides) nor a phenylselenylation (with PhSeX) have been obtained via preformed enolates: these reactions are reported here.



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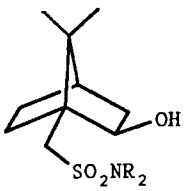

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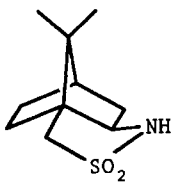

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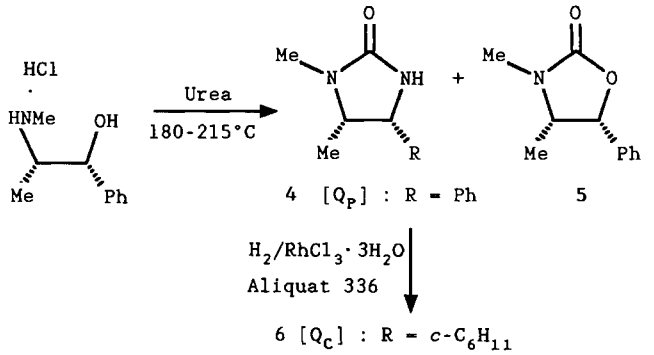
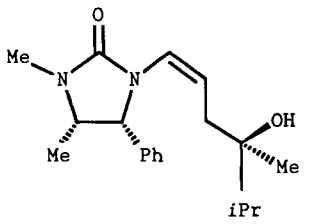
Results and Discussion

The ephedrine-imidazolidin-2-one **4** was chosen because of its ease of formation via the Close fusion method[5]. This preparation (Scheme 1) is amenable to multigram preparation (100–200 g) and the product readily crystallises from the major oxazolidin-2-one impurity **5**. By the use of efficient stirring, the yield of **4** has been consistently raised to around 60% (ref.[5] 47%).

In the original work, a 4,5-*trans* stereochemistry had been proposed for **4**. Helmchen and co-workers[6a] proved the alternative 4,5-*cis* arrangement by X-ray analysis of **7**.

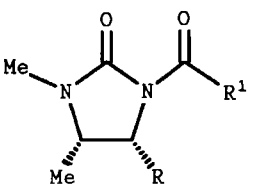
Scheme 1





7

For the conversion of **4**→**6**, the method of Blum et al.[7] proved to be the most efficient and reproducibly affords ≥95% yields. We have not carried out an accurate cost analysis for the synthesis of **4**, or its conversion to **6**, but



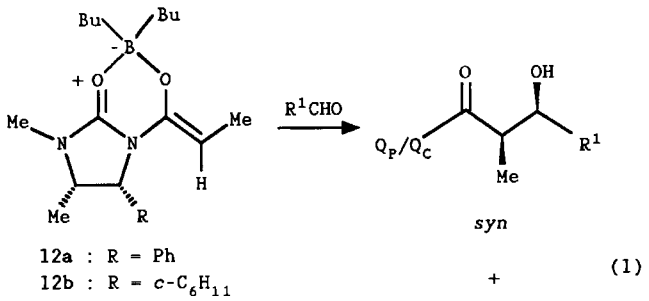
8 - 11

	R	R^1
8	Ph	Et
9	c-C_6H_{11}	Et
10	c-C_6H_{11}	Me_2CH
11	c-C_6H_{11}	Pr

the relatively cheap starting materials, coupled with the recyclability of reagents, make them an attractive addition to the synthetic chemists' armoury of chiral auxiliaries. Both auxiliaries **4** and **6** were smoothly *N*-acylated by reaction of their respective lithium salts with the appropriate acid chloride or anhydride to afford the derivatives **8**–**11**.

Aldol Reactions

Armed with the well-documented reports of aldol diastereoselectivity[8], we felt confident of kinetic (*Z*) boron enolate generation. Thus, standard conditions[9,10] were applied for the enolates of compound **12a** and **12b** (eq. 1). These conditions involved the addition of di-*n*-butylboron triflate to the *N*-acylimidazolidin-2-one at −10 °C in dry CH_2Cl_2 in the presence of triethylamine. Addition of the aldehyde took place at −78 °C, whereafter the reaction mixture was allowed to rise slowly to −10 °C before quenching with aq. phosphate buffer, MeOH, and 30% hydrogen peroxide. A study of a range of representative aldehydes gave the results shown in Table 1 and 2.



12a : R = Ph
12b : R = *c*-C_6H_{11}

(1)

	R^1
13	Ph
14	4-$NO_2C_6H_4$
15	4-$OMeC_6H_4$
21	Me
22	Me_2CH
23	*c*-C_6H_{11}
24	Ph

13-15 and 21-24

Inspection reveals that diastereoselectivity is high for the aromatic aldehydes, but a marked decrease is observed with the other examples. These results may be interpreted in terms of both electronic and steric factors. Figure 1 shows the *Z*-enolate with carbonyl functionalities in the preferred dipolar orientation[1b] with the phenyl ring as the steric control element. The phenyl ring appears to function efficiently in this role for R = Ar, and in these cases the reaction proceeds through TS_A to afford the "Evans *syn*" product[1b]. For the non-aromatic cases, reaction via TS_B becomes viable to give the "non-Evans *syn*" as the predominant isomeric component of the minor diastereomer mixture (from coupling constants). Although not isolated, the *syn* configuration was assigned to the major diastereomer (in the mixture of minor components) on the basis of discernable proton couplings.

In these instances the diastereoselectivity is observed to improve as R^1 increases in bulk. This trend, along with the result for acrolein, would imply that the phenyl operates ineffectively as a purely steric element and that an electronic influence is also involved. We propose that for R^1 = Ar, α-face attack occurred whilst β-face attack was precluded not only on steric grounds but also as a result of repulsive π-

Table 1. Details of the aldol reaction of the boron enolates **12a** und **12b** with R^1CHO[a]

Boron enolate	Cpd.	R^1	Major *syn* isomer: Others	de[b]	mp (°C)	Yield (%)[b]
12a	13	Ph	98 : 2	>99[c]	135–136	88
12a	14	4-O_2N-C_6H_4	96 : 4	>99	156–157	85
12a	15	4-MeO-C_6H_4	96 : 4	>99	181–182	92
12a	16	Me	55 : 45	-[d]	-	-
12a	17	Et	74 : 26	-	-	-
12a	18	$CH=CH_2$	82 : 18	-	-	-
12a	19	*i*Pr	80 : 20	-	-	-
12a	20	*c*-C_6H_{11}	85 : 15	-	-	-
12b	21	Me	97 : 3	>99	-	80
12b	22	*i*Pr	>99 : 1	>99	-	82
12b	23	*c*-C_6H_{11}	>99 : 1	>99	126–127	92
12b	24	C_6H_5	98 : 2	>99	-	75

[a] Some of the above results have been reported[11a,b]. — [b] After purification by recrystallisation or flash chromatography. — [c] The absolute configuration of **13** is shown since an excellent correlation between the $[\alpha]_D$ value of its methyl ester derivative with that of a literature value was obtained. — [d] The major aldol isomers **16**–**20** were not isolated.

Table 2. ^1H- and ^{13}C-NMR data for compounds **13**, **14**, **15**, **21**, **22**, **23**, and **24**

Boron enolate	Product	$J_{A/B}$ Hz	δ-Me
12a	**13**	3.12	10.39
12a	**14**	2.47	10.00
12a	**15**	3.38	10.53
12b	**21**	2.45	11.12
12b	**22**	2.15	10.98
12b	**23**	2.00	10.90
12b	**24**	4.03	11.90

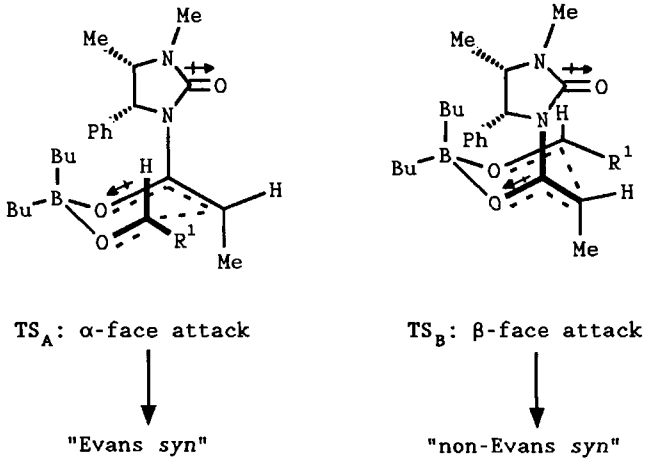
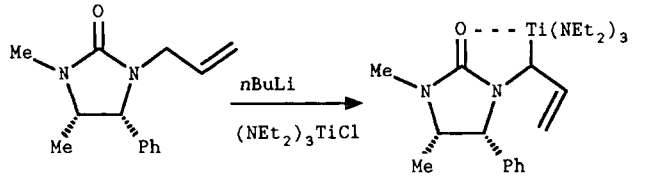
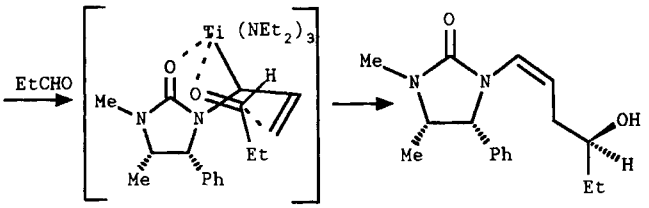


Figure 1. Proposed origins of the alternative *syn* substructures from the boron enolate **12a**

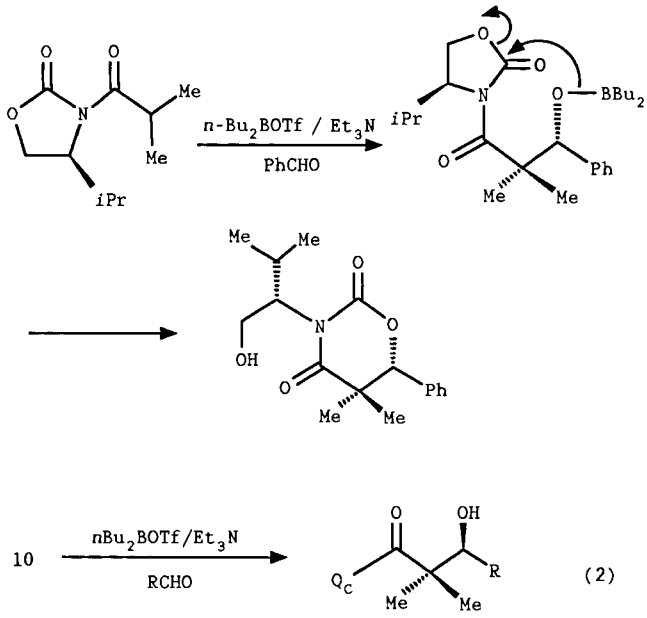
electron interactions between Ph and Ar. This argument, when applied to the acrolein example would account for the improved diastereoselectivity exhibited relative to propanal. This contrasts with the results obtained by Helmchen et al. for the diastereoselective homoaldol reaction where a very high diastereoselectivity was achieved (Scheme 2).

Scheme 2. Formation of homoaldol (Helmchen)[6a]





Scheme 3. Ring opening of oxazolidinone to form oxazinedione[13a,13b]



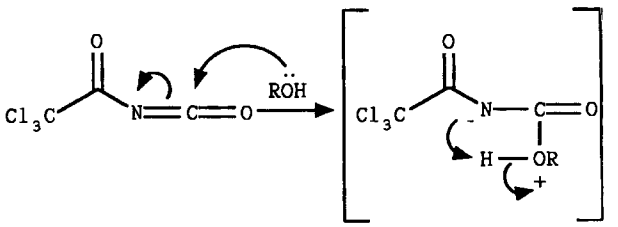
This study has shown the auxiliary **4** to be highly efficient for the aldol reactions of aromatic aldehydes. In addition, the aldol products **13**–**15** were easily recrystallised to afford single isomers. In order to extend the generality of these aldol reactions, we sought to improve the auxiliary's ability to transfer chirality. Since the results with **4** indicate that the phenyl group is moderately effective as a steric control element, hydrogenation to the more sterically demanding cyclohexyl group (Scheme 1) seemed to offer a solution. The results for cyclohexanecarboxaldehyde, as well as some literature precedents[9a,12], lent support to the above argument.

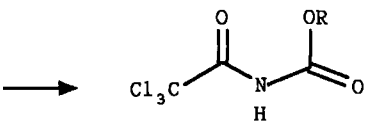
The results of the aldol reactions of the boron enolate **12b** (Table 1) show clearly the enhancement of diastereoselectivity with the non-aromatic aldehydes whilst still maintaining levels with benzaldehyde. This indicates that the 4-cyclohexyl derivative **6** is superior to **4** and is as efficient as other auxiliaries currently employed. These findings have been published in preliminary form[11].

An additional feature of our work relates to the attempted asymmetric synthesis of α,α-disubstituted β-hydroxycarbonyl units. Heathcock[13a] and Kende[13b] have both addressed this as part of natural product synthesis with the latter researchers using the Evans oxazolidinone methodology. The oxazolidinone was found to be subject to nucleophilic ring opening and afforded the corresponding oxazinedione (Scheme 3). On the basis of increased deactivation of the imidazolidinone carbonyl by the *N*-Me, we reasoned that the auxiliaries **4** and **6** should resist similar nucleophilic attack. This indeed proved to be the case, and normal aldol reaction ensued (eq. 2).

Determination of Diastereoselectivity

In order to assess rapidly the efficiency of the above auxiliaries, it was desirable to have a method which was amenable to analysis for use on crude reaction mixtures. The most popular methods in current use are NMR-based[14a] and generally require purified material. In the early part of this work, the diastereomeric ratio determinations were determined by a combination of ^{1}H NMR (benzylic proton or *N*-Me of auxiliary **4**), GC/MS of TMS ether derivatives, and ^{19}F NMR (trifluoroacetyl derivatives). Our recent adaptation of a previously published NMR procedure[14b] based on the in situ derivatisation with $Cl_3C(=O)–N=C=O$[15] proved so successful that it became the method of choice (eq. 3).





This has provided a rapid alternative procedure whereby the carbamate NH singlet (δ = 8–10) is used for accurate analysis[15a] (Table 3). In addition, this methodology allows for the assignment of relative (*syn*:*anti*) stereosubstructure[15b]. This is based on the general observation that δ_{NH} *syn* > δ_{NH} *anti*, and this was used in a complementary fashion to the ^{1}H- and ^{13}C-analysis protocol of Heathcock[16].

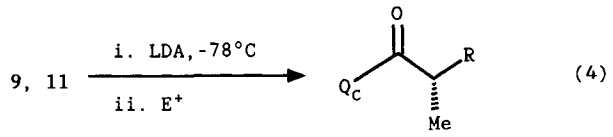
Table 3. Comparative diastereomeric ratios obtained by various analytical methods

Compound mixture	Diastereomeric ratio (major:others) ^{1}H NMR	GC/MS	^{19}F NMR	TAI
13	98 : 2	98 : 2[a]	99 : 1	98:2
14	95 : 5	-	-	96:4
15	96 : 4	-	-	96:4
17	75 : 25	-	72 : 28	74:26

[a] Carried out on the TMS ether **13a**.

Alkylation and Acylation

Whilst Cardillo et al.[6b,c] has exploited the auxiliary **4** in alkylation reactions, it was of interest to compare the efficiency of **6** in a similar sequence. This study was extended to encompass acylations (eq. 4), and the results are collected in Table 4.



(4)

	27	28	29	30	31	32	33
R	$PhCH_2$	n-octyl	allyl	PhCO	MeCO	EtCO	PhSe

Table 4. Results of alkylation/acylation reactions

Product	Electrophile	Major:Minor[a]	Yield %[b]
27	$PhCH_2Br$	>99:1(96:4)[c]	85
28	n-$C_8H_{17}Br$	>99:1(97:3)	83
29	CH_2=$CHCH_2Br$	>99:1	90
30	PhCOCl	>99:1	87
31	MeCOCl	>98:2	80
32	EtCOCl	>99:1	85
33	PhSeCl	>99:1	66

[a] These ratios were determined by ^{1}H-NMR spectroscopy and confirmed by GC/MS for **27**, **31**, and **32**. — [b] The products were purified by recrystallization or in the case of **28**, **29**, and **33** by chromatography. — [c] The ratios in parenthesis are those obtained by Cardillo et al.[6] with the 4-phenyl auxiliary **4**.

Improvements in the diastereoselectivities over those reported were indeed obtained. An interesting diastereoselectivity vs C-4 substituent study carried out by Evans[17] confirmed the relative inefficiency of the phenyl ring as a steric control element in alkylations via the related oxazolidinones.

Non-destructive Auxiliary Removal

In the cases of the aldol products **13**–**15** and **21**–**24**, treatment with freshly prepared sodium methoxide[2] afforded the corresponding β-hydroxy esters **34**–**39** by transesterification together with recovered auxiliary (Scheme 4). The α-disubstituted aldol products **25** and **26** undergo a retroaldol reaction under these conditions, probably due to steric crowding which renders attack at the carbonyl difficult. The alkylation products **27** and **28** were cleaved by reduction with $LiAlH_4$[6b] to give the alcohols **40** and **41**, whilst **29**, because of workup problems, was cleaved with $BzlO^-Li^+$ and isolated as the benzyl ester **42** (Scheme 4). Besides effecting auxiliary removal, these cleavage procedures allowed assignment of the absolute configurations, either by comparison with literature rotations data or by inference (Table 5).

Scheme 4

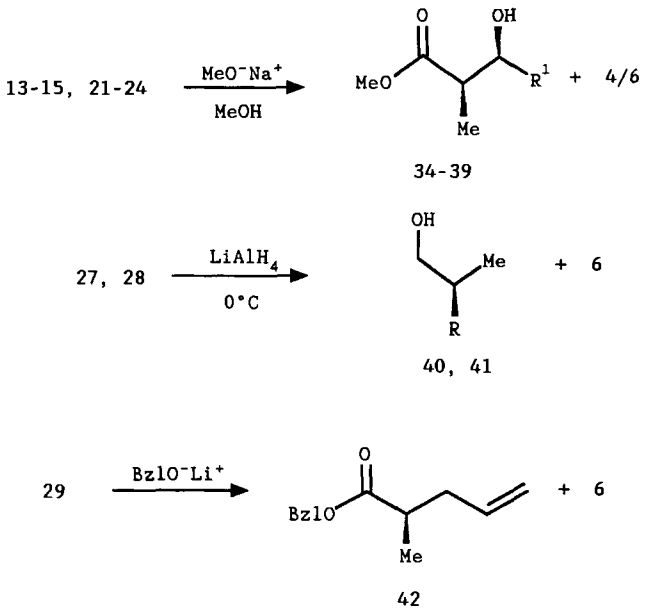
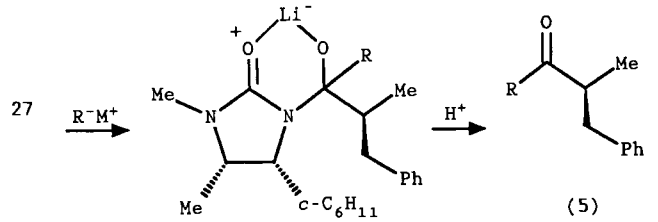


Table 5. Specific rotations of β-hydroxymethyl esters **34**–**39** (Scheme 4)

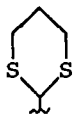
Ester	Config.	$[\alpha]_D$ Exptl.	(c. solvent) Lit.
34	2R,3R	+23.2(1.50,$CHCl_3$)	+23.2(3.20,$CHCl_3$)
35	2R,3R	+14.3(1.30,$CHCl_3$)	-
36	2R,3R	+16.9(0.13,$CHCl_3$)	-
37	2R,3S	-13.4(0.51,MeOH)	-13.5(0.87,MeOH)
38	2R,3S	+7.6(1.21,$CHCl_3$)	+7.7(5.40,$CHCl_3$)
39	2R,3S	-6.17(1.10,CH_2Cl_2)	-

An attempt to deprotonate **9** with BuLi resulted in auxiliary cleavage to afford the corresponding butyl ketone and the dibutyl tertiaryl alcohol. This prompted an investigation into the possible use of these auxiliaries for access to homochiral α-substituted ketone synthesis by direct displacement. Existing methods for the synthesis of these useful fragments largely centre around manipulations of chiral hydrazone derivatives[18]. The Evans group, in their synthesis of ferensimycin B by the oxazolidinone methodology[19], required a ketone which was obtained via the Weinreb amide[20]. Because of the additional electron donor effect of the *N*-Me in our system, it was thought that organometallic attack might proceed via a chelated Weinreb-like equivalent and thus preclude formation of the tertiary alcohol (eq. 5).



The results of this preliminary study are reported in Table 6 and indicate that the initial supposition was unfounded. Substrate **27**, whilst showing no reactivity toward Grignard reagents, is very susceptible to lithium nucleophiles, even at low temperature (−90°C). Only in the case of the severely hindered dithiane nucleophile did the reaction afford the ketone as sole product. Because of the potential utility of the ketone products, further investigation of this problem is being conducted.

Table 6. Attempted ketone synthesis from compound **27**

R	M	Ketone (%)	Alcohol (%)
Et	MgBr	-	-
PhC≡C	MgBr	-	-
PhC≡C	Li	-	**43** (42)
*n*Bu	Li	-	**44** (40)
	Li	**45** (64)	-

Conclusion

The ephedrine-derived imidazolidin-2-one auxiliaries **4** and **6** have been shown to be efficient chiral diastereoselective controllers. The steric power of the cyclohexyl group in **6** was particularly effective. There are a number of general features which recommend their addition to the pool of practically useful agents for asymmetric synthesis: viz. crystallinity of most of their products; ease of purification of adducts by either recrystallisation or flash chromatography; preparation from readily available and relatively cheap starting materials; removal by non-destructive methods; lack of susceptibility to nucleophilic ring opening. Proof of this is provided by the observation that two large manufactures are now producing **4** commercially[21].

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Experimental

Melting points (uncorrected): Kofler hot-stage. – Specific rotations: Perkin-Elmer Model 241 polarimeter. – IR: Shimadzu FTIR-4300. – ^{1}H and ^{13}C NMR: Varian Gemini (200 MHz); TMS as internal standard and $CDCl_3$ as solvent. – Elemental analyses: Perkin-Elmer 2400 and 240 B Elemental analysers. – GC/MS: Hewlett-Packard 5890 gas chromatograph/5988 A mass spectrometer; Varian high resolution mass spectrometer. – Preparative column chromatography was performed using the technique of Still et al.[22] – The imidazolidin-2-one derivatives were best visualised on TLC plates by using the cobalt(II) thiocyanate dip reagent[23]. Low reaction temperatures were maintained as described by Phipps and Hume[24].

(4R,5S)-1,5-Dimethyl-4-phenylimidazolidin-2-one (**4**): (−)-Ephedrine hydrochloride (50.00 g, 247.8 mmol) and urea (45.00 g, 750 mmol) were heated for 30 min at 170–175°C. The resultant melt was further heated at 200–210°C with magnetic stirring for 1 h. The mixture was cooled to 100°C, then treated with H_2O. The oily solid which formed was first washed with aq. HCl (5%) and then with H_2O. Recrystallization from ethanol afforded 28.80 g (60%) of **4** as white crystals, m.p. 177°C (ref.[6a] 177–179°C). $[\alpha]_D^{25} = -44.30$ (c = 0.90 in MeOH) {ref.[6a] $[\alpha]_D^{25} = -44.50$ (c = 3.00 in MeOH)}. – IR ($CHCl_3$): $\tilde{\nu}$ = 3460 cm^{-1} (NH), 1704 (CO). – ^{1}H NMR ($CDCl_3$): δ = 0.73 (d, J = 6.5 Hz, 3H, 5-Me), 2.72 (s, 3H, NMe), 3.86 (dq, 1H, J = 9.0, 6.5 Hz, 5-H), 4.77 (d, 1H, J = 9.0 Hz, 4-H), 5.70 (br s, 1H, NH), 7.24–7.38 (m, 5H, aromatic H). – ^{13}C NMR ($CDCl_3$): δ = 14.30 (q, 5-Me), 28.22 (q, NMe), 57.74 and 58.25 (d, C-5, -4), 127.55, 128.25 and 128.77 (d, aromatic CH), 138.73 (s, aromatic C), 163.22 (s, C-2). – MS (70 eV), m/z (%): 190 (62) [M$^+$], 175 (100), 58 (43). – $C_{11}H_{14}N_2O$ (190.2): calcd. C 69.45, H 7.42, N 14.72; found C 69.51, H 7.48, N 14.70.

(4R,5S)-4-Cyclohexyl-1,5-dimethylimidazolidin-2-one (**6**): A teflon reaction vessel was charged with a mixture of $RhCl_3 \cdot 3\ H_2O$ (0.26 g, 1.26 mmol) in water (30 ml), Aliquat 336 (0.58 g, 1.44 mmol), and **4** (5.00 g, 26.32 mmol) in 1,2-dichloroethane (30 ml). The reaction mixture was stirred at 30°C for 24 h under 5 at of H_2 pressure in an autoclave. The phases were separated, and the organic phase was filtered through acidic alumina, treated with activated charcoal, filtered, and concentrated. Recrystallization from ethyl acetate afforded 4.90 g (95%) of **6** as off-white crystals, m.p. 162°C. $[\alpha]_D^{25} = -1.00$ (c = 0.60 in $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3220 cm^{-1} (NH), 2952 (Me), 1691 (CO). – ^{1}H NMR ($CDCl_3$): δ = 0.82–1.82 (m, 11H, *c*-C_6H_{11}), 1.10 (d, 3H, J = 6.0 Hz, 5-Me), 2.75 (s, 3H, NMe), 3.29 (ddd, 1H, J = 2.0, 7.0, 9.0 Hz, 4-H), 3.60 (dq, 1H, $J_a = J_b$ = 7 Hz, 5-H); 5.02 (br s, 1H, NH). – ^{13}C NMR ($CDCl_3$): δ = 10.65 (q, 5-Me), 25.56, 25.59 and 26.22 (t, 3 CH_2), 27.91 (q, NMe), 29.65 and 29.92 (t, 2 CH_2), 37.12 (d, ring CH), 56.02 and 59.79 (d, C-5, -4) 162.47 (s, C-2). – MS (70 eV), m/z (%): 196 (9) [M$^+$], 113 (100). – $C_{11}H_{20}N_2O$ (196.3): calcd. C 67.31, H 10.27, N 14.27; found C 67.14, H 10.15, N 14.22.

General Procedure 1: Preparation of 3-Acylimidazolidin-2-ones **8**–**11**: A stirred solution of the appropriate imidazolidin-2-one (1 equiv.) in dry THF (30 ml) was treated with an equimolar amount of *n*-BuLi at 0°C. After 30 min at 0°C the appropriate acyl chloride or anhydride (1 equiv.) was added. The reaction mixture was stirred for 1 h at 0°C then quenched with saturated $NaHCO_3$. The THF was removed under reduced pressure, and the residue was partitioned between H_2O and CH_2Cl_2. The organic phase was dried ($MgSO_4$), concentrated and purified.

(4R,5S)-1,5-Dimethyl-4-phenyl-3-propanoylimidazolidin-2-one (**8**): Reaction of the lithium salt of **4** (5.00 g, 26.3 mmol) with propionyl chloride (2.29 ml, 26.30 mmol) according to General Procedure 1 afforded 6.15 g (95%) of **8** as white crystals, m.p. 106°C ($CHCl_3$) (ref.[6b] 90°C), $[\alpha]_D^{25} = -54.10$ (c = 1.00 in CH_2Cl_2) {ref.[6b] $[\alpha]_D = -54.70$ (c = 1.00 in CH_2Cl_2)}. – IR ($CHCl_3$): $\tilde{\nu}$ = 1728 cm^{-1} (CO), 1685 (CO). – ^{1}H NMR ($CDCl_3$): δ = 0.80 (d, 3H, J = 7.0 Hz, 5-Me), 1.10 (t, 3H, J = 7.0 Hz, 3′-H), 2.82 (s, 3H, NMe), 2.99 (q, 2H, J = 7.0 Hz, 2′-H), 3.90 (dq, 1H, J = 9, 7 Hz, 5-H), 5.29 (d, 1H, J = 9 Hz, 4-H), 7.12–7.34 (m, 5H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 8.62 (q, C-3′), 14.92 (q, 5-Me), 28.17 (t, C-2′), 29.34 (q, NMe), 54.10 and 59.38 (d, C-5, -4), 127.27, 128.32 and 128.80 (d,

aromatic CH), 137.28 (s, aromatic C), 156.42 (s, C-2), 173.86 (s, C-1'). – MS (70 eV), *m/z* (%): 246 (35) [M^+], 217 (0.7), 189 (47), 132 (100). – $C_{14}H_{18}N_2O_2$ (246.3): calcd. C 68.27, H 7.37, N 11.37; found C 68.38, H 7.66, N 11.28.

(4R,5S)-4-Cyclohexyl-1,5-dimethyl-3-propanoylimidazolidin-2-one (**9**): Reaction of the lithium salt of **6** (5.00 g 25.50 mmol) with propionyl chloride (2.22 ml, 25.50 mmol) according to General Procedure 1 afforded 6.10 g (95%) of **9** as colourless crystals, m.p. 99–100°C (hexane), $[\alpha]_D^{25} = -14.20$ (*c* = 0.16 in $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 2950 cm^{-1} (Me), 1720 (CO), 1681 (CO). – ^1H NMR ($CDCl_3$): δ = 0.82–1.36 and 1.52–1.82 (m, 11 H, *c*-C_6H_{11}), 1.17 (t, 3 H, *J* = 7 Hz, 3'-H), 1.32 (d, 3 H, *J* = 7 Hz, 5-Me), 2.76 (s, 3 H, NMe), 2.86 (dq, 1 H, *J* = 17, 7 Hz, 2'-H), 3.03 (dq, 1 H, *J* = 17, 7 Hz, 2'-H), 3.67 (dq, 1 H *J* = 7 Hz, 5-H), 4.33 (dd, 1 H, *J* = 3, 7 Hz, 4-H). – ^{13}C NMR ($CDCl_3$): δ = 9.09 (q, 5-Me), 13.08 (q, C-3'), 26.19, 26.33 and 26.97 (t, 3 CH_2), 27.75 (q, NMe), 27.75 and 29.29 (t, 2 CH_2), 32.56 (t, C-2'), 39.19 (d, ring CH), 54.84 and 59.07 (d, C-5, -4), 156.60 (s, C-2), 174.29 (s, C-1'). – MS (70 eV), *m/z* (%): 252 (12) [M^+], 223 (33), 195 (8), 113 (100). – $C_{14}H_{24}N_2O_2$ (252.4): calcd. C 66.63, H 9.58, N 11.10; found C 66.39, H 9.75, N 11.04.

(4R,5S)-4-Cyclohexyl-1,5-dimethyl-3-(2-methylpropanoyl)imidazolidin-2-one (**10**): Reaction of the Lithium salt of **6** (5.00 g, 25.50 mmol) with isobutyric anhydride (4.23 ml, 25.50 mmol) as in General Procedure 1 afforded 6.00 g (88%) of **10** as a colourless oil, $[\alpha]_D^{25} = -8.22$ (*c* = 1.00 in $CHCl_3$). – IR (neat): $\tilde{\nu}$ = 2960 cm^{-1} (Me), 1736 (CO), 1692 (CO). – ^1H NMR ($CDCl_3$): δ = 1.10 (d, 3 H, *J* = 7 Hz, 3'-H), 1.25 (d, 3 H, *J* = 7 Hz, 3''-H), 1.33 (d, 3 H, *J* = 7 Hz, 5-Me), 0.95–1.85 (m, 11 H, *c*-C_6H_{11}), 2.77 (s, 3 H, NMe), 3.69 (dq, 1 H, $J_a = J_b$ = 7 Hz, 5-H), 3.88 (dq, 1 H, *J* = 7 Hz, 2'-H), 4.36 (dd, 1 H, *J* = 7, 3 Hz, 4-H). – ^{13}C NMR ($CDCl_3$): δ = 12.98 (q, 5-Me), 18.39, 20.49 (2 q, C-3' and C-3''), 26.10, 26.26, 26.92, 27.59 (t, 4 CH_2), 27.67 (q, NMe), 32.55 (t, CH_2), 32.65 (d, C-2'), 39.17 (d, ring CH), 54.48 and 58.65 (d, C-5, -4), 156.13 (s, C-2), 177.66 (s, C-1'). – MS (70 eV), *m/z* (%): 266 (2) [M^+], 223 (8), 183 (9), 113 (100). – $C_{15}H_{26}N_2O_2$: calcd. 266.1994; found 266.1980 (MS).

(4R,5S)-3-Butanoyl-4-cyclohexyl-1,5-dimethylimidazolidin-2-one (**11**): Reaction of the lithium salt of **6** (5.00 g, 25.50 mmoL) with *n*-butyric anhydride (4.17 ml, 25.50 mmol) according to General Procedure 1 afforded 6.20 g (91%) of **11** as white crystals, m.p. 77°C ($CHCl_3$), $[\alpha]_D^{25} = -14.93$ (*c* = 1.42 in $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 2960 cm^{-1} (Me), 2860 (CH_2), 1724 (CO), 1676 (CO). – ^1H NMR ($CDCl_3$): δ = 0.98 (t, 3 H, *J* = 7 Hz, 4'-H), 1.00–1.85 (m, 13 H, *c*-C_6H_{11} and 3'-H), 1.33 (d, 3 H, *J* = 7 Hz, 5-Me), 2.76 (s, 3 H, NMe), 2.78 (ddd, 1 H, *J* = 7, 8, 16 Hz, 2'-H), 3.04 (ddd, 1 H, *J* = 7, 8, 16 Hz, 2'-H), 3.68 (dq, 1 H, $J_a = J_b$ = 7 Hz, 5-H), 4.34 (dd, 1 H, *J* = 4, 7 Hz, 4-H). – ^1H NMR ($CDCl_3$): δ = 13.08 (q, C-4'), 13.89 (q, 5-Me), 18.49, 26.10, 26.18, 26.89, 27.67, 32.49 and 37.61 (t, 5 ring CH_2, C-2' and C-3'), 27.67 (q, NMe), 39.06 (d, ring CH), 54.62 and 58.80 (d, C-5, -4), 156.53 (s, C-2), 173.34, (s, C-1'). – MS (70 eV), *m/z* (%): 266 (3) [M^+], 223 (7), 113 (100). – $C_{15}H_{26}N_2O_2$ (266.2): calcd. C 67.62, H 9.84, N 10.52; found C 67.48, H 10.02, N 10.65.

General Procedure 2: Preparation of the Aldol Products **13–26**: To a stirred, cold (–10°C) solution of the appropriate *N*-acylimidazolidin-2-one (1.00 equiv.) in dry CH_2Cl_2 (4 ml) was added dropwise over 1 min di-*n*-butylboron triflate (1 M in CH_2Cl_2, 1.15 equiv.). After 5 min Et_3N (1.30 equiv.) was added. The mixture was stirred at –10°C for 1 h, cooled to –78°C, and the appropriate aldehyde (1.00 equiv.) was added. After 30 min at –78°C the reaction temp. was allowed to rise to –10°C and maintained at this temperature for 1 h. The reaction was then quenched by sequential addition of aq. pH 7 phosphate buffer (4.5 ml), MeOH (16.5 ml), and 30% H_2O_2 (4.5 ml) in MeOH (8.5 ml). After 1 h at 0°C the mixture was concentrated and the residue partitioned between Et_2O and H_2O. The organic phase was sequentially washed with cold HCl (5%) satd. aq. $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$) and concentrated.

(4R,5S,2'R,3'R)-3-(3-Hydroxy-2-methyl-3-phenylpropanoyl)-1,5-dimethyl-4-phenylimidazolidin-2-one (**13**): The boron enolate of **8** (1.00 g, 4.10 mmol) was allowed to react with benzaldehyde (0.41 ml, 4.06 mmol) according to General Procedure 2 to afford 1.26 g (88%) of **13** as white crystals, m.p. 135–136°C (C_6H_6), $[\alpha]_D^{25} = -35.30$ (*c* = 0.60 in $CHCl_3$). – IR ($CHCl_3$): $\tilde{\nu}$ = 3500 cm^{-1} (OH), 1730 (CO), 1660 (CO), 1605 (Ph). – ^1H NMR ($CDCl_3$): δ = 0.76 (d, 3 H, *J* = 7 Hz, 5-Me), 1.07 (d, 3 H, *J* = 7 Hz, 2'-Me), 2.79 (s, 3 H, NMe), 3.75 (d, 1 H, OH, D_2O exch.), 3.81 (dq, 1 H, *J* = 7, 9 Hz, 5-H), 4.28 (dq, 1 H, *J* = 7, 3 Hz, 2'-H), 5.10 [m, 1 H, 3'-H (D_2O exch., d, *J* = 3 Hz)], 5.28 (d, 1 H, *J* = 9 Hz, 4-H), 7.10–7.43 (m, 10 H, 2 Ph). – ^{13}C NMR ($CDCl_3$): δ = 10.39 (q, 2'-Me), 14.98 (q, 5-Me), 28.24 (q, NMe), 44.24 (d, C-2'), 53.80 and 59.29 (d, C-5, -4), 73.49 (d, C-3'), 126.51, 127.02, 127.41, 128.38, 128.60 and 129.03 (d, Ph), 136.74 and 142.01 (s, Ph), 155.57 (s, C-2), 177.44 (s, C-1'). – MS (70 eV), *m/z* (%): 352 (10) [M^+], 334 (2), 246 (100). – $C_{21}H_{24}N_2O_3$: calcd. 352.1786; found 352.1755 (MS).

(4R,5S,2'R,3'R)-3-[3-Hydroxy-2-methyl-3-(4-nitrophenyl)propanoyl]-1,5-dimethyl-4-phenylimidazolidin-2-one (**14**): The boron enolate of **8** (1.00 g, 4.06 mmol) was allowed to react with 4-nitrobenzaldehyde (0.16 g, 4.06 mmol) according to General Procedure 2 to afford 1.37 g (85%) of **14** as pale yellow crystals, m.p. 156–157°C (C_6H_6), $[\alpha]_D^{25} = -28.00$ (*c* = 0.60 in $CHCl_3$). – IR ($CHCl_3$): $\tilde{\nu}$ = 3500 cm^{-1} (OH), 1732 (CO), 1658 (CO), 1603 (Ph), 1520 and 1348 (C–NO_2). – ^1H NMR ($CDCl_3$): δ = 0.82 (d, 3 H, *J* = 7 Hz, 5-Me), 1.02 (d, 3 H, *J* = 7 Hz, 2'-Me), 2.86 (s, 3 H, NMe), 3.96 (dq, 1 H, *J* = 9, 7 Hz, 5-H), 4.06 (d, 1 H, OH, D_2O exch.), 4.29 (dq, 1 H, *J* = 7, 2.5 Hz, 2'-H), 5.23 [m, 1 H, 3'-H (D_2O exch., d, *J* = 2.5 Hz)], 5.37 (m, 1 H, *J* = 9 Hz, 4-H), 7.28–7.40 (m, 5 H, Ph), 7.57–8.22 (m, 4 H, Ar). – ^{13}C NMR ($CDCl_3$): δ = 10.00 (q, 2'-Me), 15.07 (q, 5-Me), 29.34 (q, NMe), 43.76 (d, C-2'), 53.92 and 59.29 (d, C-5, -4), 72.55 (d, C-3'), 123.70, 126.99, 127.40, 128.78, and 129.15 (d, Ar and Ph), 136.51, 147.48, and 149.51 (s, Ar and Ph), 155.49 (s, C-2), 177.07 (s, C-1'). – MS (70 eV), *m/z* (%): 397 (6) [M^+], 246 (100), 189 (67). – $C_{21}H_{23}N_3O_5$: calcd. 397.1637; found 397.1649 (MS).

(4R,5S,2'R,3'R)-3-[3-Hydroxy-2-methyl-3-(4-methoxyphenyl)-propanoyl]-1,5-dimethyl-4-phenylimidazolidin-2-one (**15**): The boron enolate of **8** (1.00 g, 4.06 mmol) was allowed to react with 4-methoxybenzaldehyde (0.55 g, 4.06 mmol) as in General Procedure 2 to afford 1.43 g (92%) of **15** as white crystals, m.p. 181–182°C ($CHCl_3$), $[\alpha]_D^{25} = -40.00$ (*c* = 0.11 in $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3482 cm^{-1} (OH), 2987 (Me), 1732 (CO), 1674 (CO), 1606 and 1510 (Ph). – ^1H NMR ($CDCl_3$): δ = 0.77 (d, 3 H, *J* = 7 Hz, 5-Me), 1.08 (d, 3 H, *J* = 7 Hz, 2'-Me), 2.80 (s, 3 H, NMe), 3.65 (m, 1 H, OH, D_2O exch.), 3.78 (s, 3 H, OMe), 3.82 (dq, 1 H, *J* = 9, 7 Hz, 5-H), 4.24 (dq, 1 H, *J* = 7, 3.4 Hz, 2'-H), 5.05 [m, 1 H, 3'-H (D_2O exch., d, *J* = 3.4 Hz)], 5.27 (d, 1 H, *J* = 9 Hz, 4-H), 6.83–7.34 (m, 9 H, Ph and Ar). – ^{13}C NMR ($CDCl_3$): δ = 10.53 (q, 2'-Me), 14.96 (q, 5-Me), 28.18 (q, NMe), 44.22 (d, C-2'), 53.65 (d, C-5), 55.22 (q, OMe), 59.12 (d, C-4), 73.01 (d, C-3'), 113.37, 126.63, 127.54, 128.19, and 128.63 (d, Ar and Ph), 133.82, 136.36, and 155.15 (s, Ar and Ph), 158.61 (s, C-2), 176.87 (s, C-1'). – MS (70 eV), *m/z* (%): 382 (3) [M^+], 364 (3), 246 (100), 189 (55). – $C_{22}H_{26}N_2O_4$: calcd. 382.1892; found 382.1813 (MS).

(4R,5S,2'R,3'S)-4-Cyclohexyl-3-(3-hydroxy-2-methylbutanoyl)-1,5-dimethylimidazolidin-2-one (**21**): Th reaction between the boron enolate of **9** (1.00 g, 3.97 mmol) and acetaldehyde (0.22 ml, 3.97

mmol) according to General Procedure 2 yielded a residue which was purified by flash chromatography [diethyl ether/hexane (3:7)] to afford 0.94 g (80%) of **21** as a colourless oil, $[\alpha]_D^{25} = -2.20$ (c = 1.064 in $CHCl_3$). – IR (neat): $\tilde{\nu}$ = 3495 cm^{-1} (OH), 2930 (CH_2), 1730 (CO), 1678 (CO). – ^1H NMR ($CDCl_3$): δ = 0.95–1.85 (m, 11H, c-C_6H_{11}), 1.16 (d, 3H, J = 6.5 Hz, 2′-Me), 1.30 (d, 3H, J = 7 Hz, 4′-H), 1.34 (d, 3H, J = 7 Hz, 5-Me), 2.78 (s, 3H, NMe), 3.71 (dq, 1H, $J_a = J_b$ = 7 Hz, 5-H), 3.62–3.80 (br s, 1H, OH), 3.80 (dq, 1H, J = 7, 2.5 Hz, 3′-H), 4.12 (dq, 1H, J = 6.5, 2.5 Hz, 2′-H), 4.39 (dd, 1H, J = 3, 7 Hz, 4-H). – ^{13}C NMR ($CDCl_3$): δ = 11.12 (q, 2′-Me), 12.92 (q, C-4′), 19.39 (q, 5-Me), 26.11, 26.26, 26.94, and 27.64 (t, 4 CH_2), 27.76 (q, NMe), 32.65 (t, CH_2), 39.27 (d, ring CH), 43.03 (d, C-2′), 54.57 and 58.71 (d, C-5, -4), 67.53 (d, C-3′), 155.89 (s, C-2), 178.11 (s, C-1′). – MS (70 eV), m/z (%): 296 (2) [M^+], 252 (2), 223 (12), and 113 (100). – $C_{16}H_{26}N_2O_3$: calcd. 296.2099; found 296.2056 (MS).

(4R,5S,2′R,3′S)-4-Cyclohexyl-3-(3-hydroxy-2,4-dimethylpentanoyl)-1,5-dimethylimidazolidin-2-one (**22**): The reaction between the boron enolate of **9** (1.00 g, 3.97 mmol) and isobutyraldehyde (0.36 ml, 3.97 mmol) according to General Procedure 2 yielded a residue which was purified by flash chromatography [diethyl ether/hexane (1:1)] to afford 1.05 g (82%) of **22** as a colourless oil, $[\alpha]_D^{25} = +2.57$ (c = 0.62 in $CHCl_3$). – IR (neat): $\tilde{\nu}$ = 3500 cm^{-1} (OH), 2960 (Me), 1730 (CO), 1670 (CO). – ^1H NMR ($CDCl_3$): δ = 0.88 (d, 3H, J = 7 Hz, 4′-Me), 1.03 (d, 3H, J = 7 Hz, 5′-H), 0.92–1.32 and 1.52–1.82 (m, 11H, c-C_6H_{11}), 1.27 (d, 3H, J = 7 Hz, 2′-Me), 1.34 (d, 3H, J = 7 Hz, 5-Me), 1.72 (2 dq, 1H, J = 9, 7 Hz, 4′-H), 2.78 (s, 3H, NMe), 3.45 (ddd, 1H, J = 2, 2, 9 Hz, 3′-H), 3.71 (dq, 1H, $J_a = J_b$ = 7 Hz, 5-H), 3.76 (d, 1H, J = 2 Hz, OH), 4.08 (dq, 1H, J = 7, 2 Hz, 2′-H), 4.39 (dd, 1H, J = 3, 7 Hz, 4-H). – ^{13}C NMR ($CDCl_3$): δ = 10.98 (q, 2′-Me), 12.96 (q, 5-Me), 18.92 (q, 4′-Me), 19.63 (q, C-5′), 26.06, 26.19, 26.87 and 27.58 (t, 4 CH_2), 27.70 (q, NMe), 30.36 (d, C-4′), 32.49 (t, CH_2), 39.10 (d, ring CH), 39.20 (d, C-2′), 54.34 and 58.42 (d, C-5, -4), 76.60 (d, C-3′), 155.67 (s, C-2), 178.72 (s, C-1′). – MS (70 eV), m/z (%). 324 (6) [M^+], 306 (7), 252 (51), 223 (70), 113 (100). – $C_{18}H_{32}N_2O_3$: calcd. 324.2413; found 324.2390 (MS).

(4R,5S,2′R,3′S)-4-Cyclohexyl-3-(3-cyclohexyl-3-hydroxy-2-methylpropanoyl)-1,5-dimethylimidazolidin-2-one (**23**): The reaction between the boron enolate of **9** (1.00 g, 3.97 mmol) and cyclohexanecarbaldehyde (0.48 ml, 3.97 mmol) as in General Procedure 2 yielded 1.33 g (92%) of **23** as cream-coloured crystals, m.p. 126–128°C (hexane), $[\alpha]_D^{25} = -7.84$ (c = 1.12 in $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3500 cm^{-1} (OH), 2920 (CH_2), 1725 (CO), 1650 (CO). – ^1H NMR ($CDCl_3$): δ = 0.80–1.82 (m, 21H, 2 c-C_6H_{11}), 1.26 (d, 3H, J = 7 Hz, 2′-Me), 1.33 (d, 3H, J = 7 Hz, 5-Me), 2.08–2.22 (m, 1H, ring CH), 2.77 (s, 3H, NMe), 3.52 (ddd, 1H), J = 2, 2, 9 Hz, 3′-H), 3.71 (dq, 1H, $J_a = J_b$ = 7 Hz, 5-H), 3.76 (d, 1H, J = 2 Hz, OH), 4.06 (dq, 1H, J = 7, 2 Hz, 2′-H), 4.38 (dd, 1H, J = 3, 7 Hz, 4-H). – ^{13}C NMR ($CDCl_3$): δ = 10.90 (q, 2′-Me), 12.96 (q, 5-Me), 25.97, 26.06, 26.18, 26.46, 26.86, 27.57 (t, CH_2), 27.70 (q, NMe), 28.77, 29.93, and 32.49 (t, CH_2), 38.56 and 39.18 (d, 2 ring CH), 39.72 (d, C-2′), 54.34 and 58.40 (d, C-5, -4), 75.33 (d, C-3), 155.68 (s, C-2), 178.82 (s, C-1). – MS (70 eV), m/z (%): 364 (1) [M^+], 346 (3), 252 (18), 223 (27), 113 (100). – $C_{21}H_{36}N_2O_3$: calcd. 364.2726; found 364.2738 (MS).

(4R,5S,2′R,3′R)-4-Cyclohexyl-3-(3-hydroxy-2-methyl-3-phenylpropanoyl)-1,5-dimethylimidazolin-2-one (**21**): The reaction between the boron enolate of **9** (1.00 g, 3.97 mmol) and benzaldehyde (0.40 ml, 3.97 mmol) according to General Procedure 2 yielded a residue which was purified by flash chromatography [diethyl ether/hexane (3:7)] to afford 1.07 g (75%) of **24** as a colourless oil, $[\alpha]_D^{25} = -5.73$ (c = 1.00 in $CHCl_3$). – IR ($CHCl_3$): $\tilde{\nu}$ = 3500 cm^{-1} (OH), 2930 (CH_2), 1730 (CO), 1650 (CO). – ^1H NMR ($CDCl_3$): δ = 0.85–1.85 (m, 11H, c-C_6H_{11}), 1.22 (2 d, 6H, J = 7 Hz, 5-Me and 2′-Me), 2.66 (s, 3H, NMe), 3.38 (dq, 1H, $J_a = J_b$ = 7 Hz, 5-H), 4.08 (br s, 1H, OH, D_2O exch.), 4.22 (dd, 1H, J = 3, 7 Hz, 4-H), 4.23 (dq, 1H, J = 7, 4 Hz, 2′-H), 4.97 [m, 1H, 3′-H (D_2O exch., d, J = 4 Hz)], 7.19–7.39 (m, 5H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 11.90 (q, 2′-Me), 12.75 (q, 5-Me), 25.98, 26.14, and 26.80 (t, 3 CH_2), 27.49 (q, NMe), 27.49 and 32.46 (t, 2 CH_2), 38.98 (d, ring CH), 44.23 (d, C-2′), 54.14 and 58.70 (d, C-5, -4), 73.84 (d, C-3′), 126.24, 126.95, and 127.87 (d, Ph), 141.92 (s, Ph), 155.55 (s, C-2), 177.16 (s, C-1′). – MS (70 eV), m/z (%): 358 (4) [M^+], 340 (2), 252 (21), 223 (32), 113 (100). – $C_{21}H_{30}N_2O_3$: calcd. 358.2215; found 358.2255 (MS).

(4R,5S,3′R)-4-Cyclohexyl-3-(3-hydroxy-2,2-dimethyl-3-phenylpropanoyl)-1,5-dimethylimidazolidin-2-one (**25**): The boron enolate of **10** (1.00 g, 3.76 mmol) was allowed to react with benzaldehyde (0.38 ml, 3.76 mmol) according to General Procedure 2 to afford a residue which was purified by flash chromatography [diethyl ether/hexane (3:7)] as the eluent to yield 1.16 g (83%) of **25** as a colourless oil, $[\alpha]_D^{25} = +0.70$ (c = 5.79 in $CHCl_3$). – IR (neat): $\tilde{\nu}$ = 3500 cm^{-1} (OH), 2940 (CH_2), 1728 (CO), 1672 (CO). – ^1H NMR ($CDCl_3$): δ = 1.00–1.80 (m, 11H, c-C_6H_{11}), 1.29 (d, 3H, J = 7 Hz, 5-Me), 1.32 and 1.35 (2 s, 6H, 2 2′-Me), 2.75 (s, 3H, NMe), 3.46 (br s, 1H, OH), 3.67 (dq, 1H, $J_a = J_b$ = 7 Hz, 5-H), 4.49 (dd, 1H, J = 3, 7 Hz, 4-H), 5.46 (br s, 1H, 3′-H), 7.20–7.43 (m, 5H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 13.00 (q, 5-Me), 19.32 and 21.57 (q, 2 2′-Me), 26.20, 26.25, 26.90 and 27.68 (t, 4 CH_2), 27.85 (q, NMe), 32.29 (t, CH_2), 39.18 (d, ring CH), 50.79 (s, C-2′), 54.30 and 60.78 (d, C-5, -4), 76.89 (d, C-3′), 127.22, 127.42, and 128.11 (d, Ph), 140.65 (s, Ph), 155.76 (s, C-2), 178.22 (s, C-1′). – MS (70 eV), m/z (%): 372 (2) [M^+], 266 (3), 223 (13), (100). – $C_{22}H_{32}N_2O_3$: calcd. 372.2413; found 372.2426 (MS).

(4R,5S,3′S)-4-Cyclohexyl-3-(3-cyclohexyl-3-hydroxy-2,2-dimethylpropanoyl)-1,5-dimethylimidazolidin-2-one (**26**): The boron enolate of **10** (1.00 g, 3.76 mmol) was allowed to react with cyclohexanecarbaldehyde (0.46 ml, 3.76 mmol) according to General Procedure 2 to afford 0.57 g (40%) of **26** as white crystals, m.p. 141–142°C ($CHCl_3$) $[\alpha]_D^{25} = +0.75$ (c = 2.27 in $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3520 cm^{-1} (OH), 2960 (Me), 1732 (CO), 1648 (CO). – ^1H NMR ($CDCl_3$): δ = 0.80–1.95 (m, 22H, 2 c-C_6H_{11}), 1.31 (d, 3H, J = 7 Hz, 5-Me), 1.39 and 1.41 (2 s, 6H, 2 2′-Me), 2.76 (s, 3H, NMe), 3.29 (br s, 1H, OH), 3.71 (dq, 1H, $J_a = J_b$ = 7 Hz, 5-H), 3.94 (br s, 1H, 3′-H), 4.48 (dd, 1H, J = 3, 7 Hz, 4-H). – ^{136}C NMR ($CDCl_3$): δ = 13.10 (q, 5-Me), 22.19 and 22.87 (q, 2 2′-Me), 26.20, 26.27, 26.37, 26.77, and 26.94 (t, 6 CH_2), 27.77 (q, NMe), 27.84, 28.11, 32.06, and 32.93 (t, 4 CH_2), 39.32 and 40.20 (d, 2 ring CH), 54.35 and 60.95 (d, C-5, -4), 79.66 (d, C-3′), 156.02 (s, C-2), 178.46 (s, C-1). – MS (70 eV), m/z (%): 360 (1) [$M^+ - 18$], 267 (5), 223 (24), 113 (100). – $C_{22}H_{38}N_2O_3$ (378.3): calcd. C 69.79, H 10.12, N 7.40; found C 70.10, H 10.29, N 7.39.

(4R,5S,2′R,3′R)-1,5-Dimethyl-3-[2-methyl-3-phenyl-3-(trimethylsilyloxy)propanoyl]-4-phenylimidazolidin-2-one (**13a**): To a stirred solution of **13** (0.43 g, 1.23 mmol) and TMSCl (0.31 ml, 2.00 equiv.) in dry CH_2Cl_2 (10 ml) was added Et_3N (0.34 ml, 2.00 equiv.) at 0°C. After 5 h the mixture was concentrated, and the resultant residue was partitioned between Et_2O and H_2O. The organic layer was dried ($MgSO_4$) and concentrated. Recrystallisation of the resultant residue afforded 0.44 g (85%) of **13a** as colourless crystals, m.p. 152–154°C ($CHCl_3$), $[\alpha]_D^{25} = -76.35$ (c = 2.03 in $CHCl_3$). – IR ($CHCl_3$): $\tilde{\nu}$ = 2976 cm^{-1} (Me), 1728 (CO), 1678 (CO), 1232 (Si – C). – ^1H NMR ($CDCl_3$): δ = 0.02 (s, 9H, $SiMe_3$), 0.67 (d, 3H, J = 7 Hz, 5-Me), 1.18 (d, 3H, J = 7 Hz, 2′-Me), 2.68 (s, 3H, NMe), 3.34 (dq, 1H, J = 8, 7 Hz, 5-H), 4.39 (dq, 1H, J = 8, 7 Hz,

2′-H), 4.79 (d, 1H, J = 8 Hz, 3′-H), 4.89 (d, 1H, J = 8 Hz, 4-H), 7.04–7.43 (m, 10H, 2 Ph). – ^{13}C NMR ($CDCl_3$): δ = 0.01 (q, $SiMe_3$), 13.54 (q, 5-Me), 14.61 (q, 2′-Me), 27.95 (NMe), 46.61 (d, C-2′), 53.57 and 59.66 (d, C-5, -4), 76.80 (d, C-3′), 127.09, 127.29, 127.89, 128.21, and 128.72 (d, 2 Ph), 137.02 and 143.97 (s, C-2), 174.27 (s, C-1′). – MS (70 eV), m/z (%): 318 (15) [M^+ – 106], 189 (6), and 73 (100). – $C_{24}H_{32}N_2O_3Si$ (44.3): calcd. C 67.82, H 7.59, N 6.59; found C 67.89, H 7.59, N 6.60.

General Procedure 3: Diastereoselective Alkylations and Acylations: To a stirred, cooled (0°C) solution of diisopropylamine (1.05 equiv.) in dry THF (10 ml) was added dropwise *n*BuLi (1.00 equiv.). After 30 min at 0°C the reaction mixture was cooled to –78°C and treated with a THF solution of either **9** or **11** (1.00 equiv.). The reaction mixture was stirred for 30 min, then treated with the appropriate alkyl halide, acyl chloride, or anhydride (1.00 equiv.) and kept at –78°C for a further 15 min, then allowed to warm to –20°C over 30 min. The reaction was quenched with satd. aq. NH_4Cl and extracted with Et_2O. The combined extracts were dried ($MgSO_4$), concentrated and purified.

(4R,5S,2′S)-4-Cyclohexyl-1,5-dimethyl-3-(2-methyl-3-phenylpropanoyl)imidazolidin-2-one (**27**): The reaction between the lithium enolate of **9** (1.00 g, 3.97 mmo) and benzyl bromide (0.47 ml, 3.97 mmol) according to General Procedure 3 yielded 1.15 g (85%) of **27** as white crystals, m. p. 88°C (diethyl ether), $[\alpha]_D^{25}$ = +13.03 (c = 1.45 in $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 2960 cm^{-1} (Me), 1728 (CO), 1680 (CO), 1495 (Ph). – ^{1}H NMR ($CDCl_3$): δ = 0.75–1.72 (m, 1H, *c*-C_6H_{11}), 1.10 (d, 3H, J = 7 Hz, 2′-Me), 1.30 (d, 3H, J = 7 Hz, 5-Me), 2.61 (dd, 1H, J = 8, 13 Hz, 3′-H), 2.78 (s, 3H, NMe), 3.24 (dd, 1H, J = 7, 13 Hz, 3′-H), 3.65 (dq, 1H, J_a = J_b = 7 Hz, 5-H), 4.31 (m, 2H, 2′-H and 4-H), 7.12–7.39 (m, 5H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 12.96 (q, 5-Me), 16.45 (q, 2′-Me), 25.91, 25.98, 26.86, and 27.36 (t, 4 CH_2), 27.57 (q, NMe), 32.25 (t, CH_2), 39.11 (d, C-2′), 39.33 (d, ring CH), 40.57 (t, C-3′), 54.30 and 58.72 (d, C-5, -4), 126.04, 128.14, and 129.28 (d, Ph), 139.88 (s, Ph), 156.19 (s, C-2), 176.45 (s, C-1′). – MS (70 eV), m/z (%): 342 (2) [M^+], 195 (13), 113 (100), 91 (45). – $C_{21}H_{30}N_2O_2$ (342.2): calcd. C 73.63, H 8.83, N 8.18; found C 73.97, H 8.81, N 8.29.

(4R,5S,2′S)-4-Cyclohexyl-1,5-dimethyl-3-(2-methyldecanoyl)imidazolidin-2-one (**28**): The lithium enolate of **9** (1.00 g, 3.97 mmol) and octyl bromide (0.68 ml, 3.97 mmol) were allowed to react according to General Procedure 3. Purification by flash chromatography [diethyl ether/hexane (1:1)] yielded 1.20 g (83%) of **28** as a yellow oil, $[\alpha]_D^{25}$ = +0.35 (c = 2.27 in $CHCl_3$). – IR (neat): $\tilde{\nu}$ = 2940 cm^{-1} (CH_2), 1736 (CO), 1684 (CO). – ^{1}H NMR ($CDCl_3$): δ = 1.08 (d, 3H, J = 7 Hz, 2′-Me), 1.31 (d, 3H, J = 7 Hz, 5-Me), 0.82–1.95 (m, 28H, *c*-C_6H_{11} and 3′-H to 10′-H), 2.76 (s, 3H, NMe), 3.67 (dq, 1H, J_a = J_b = 7 Hz, 5-H), 3.89 (m, 1H, 2′-H), 4.38 (dd, 1H, J = 2.5, 7 Hz, 4-H). – ^{13}C NMR ($CDCl_3$): δ = 13.07 (q, 5-Me), 14.13 (q, C-10′), 16.60 (q, 2′-Me), 22.67, 26.13, 26.30, 27.00, and 27.22 (t, 5 CH_2), 27.70 (q, NMe), 29.30, 29.67, 29.75, 29.84, 31.94, 32.52, and 34.83 (t, 7 CH_2), 37.40 (d, C-2′), 39.29 (d, ring CH), 54.40 and 58.82 (d, C-5, -4), 156.28 (s, C-2), 177.50 (s, C-1′). – MS (70 eV), m/z (%): 364 (1) [M^+], 223 (12), 195 (5), 113 (100). – $C_{22}H_{40}N_2O_2$: calcd. 364.3089; found 364.3079 (MS).

(4R,5S,2′S)-4-Cyclohexyl-1,5-dimethyl-3-(2-methylpent-4-enoyl)-imidazolidin-2-one (**29**): The lithium enolate of **9** (1.00 g, 3.97 mmol) and allyl bromide (0.34 ml, 3.97 mmol) were allowed to react according to General Procedure 3. Purification by flash chromatography [diethyl ether/hexane (1:1)] yielded 1.04 g (90%) of **29** as a colourless oil, $[\alpha]_D^{25}$ = +5.66 (c = 8.75 in $CHCl_3$). – IR (neat): $\tilde{\nu}$ = 2960 cm^{-1} (Me), 1736 (CO), 1684 (CO), 920 (C=C). – ^{1}H NMR ($CDCl_3$): δ = 0.95–1.85 (m, 11H, *c*-C_6H_{11}), 1.09 (d, 3H, J = 7 Hz, 2′-Me), 1.32 (d, 3H, J = 7 Hz, 5-Me), 2.57 (m, 1H, 3′-H), 2.22 (m, 1H, 3′-H), 2.77 (s, 3H, NMe), 3.68 (dq, 1H, J_a = J_b = 7 Hz, 5-H), 3.99 (m, 1H, 2′-H), 4.37 (dd, 1H, J = 3, 7 Hz, 4-H), 5.08 (m, 2H, 5′-H), 5.87 (m, 1H, 4′-H). – ^{13}C NMR ($CDCl_3$): δ = 13.02 (q, 5-Me), 16.19 (q, 2′-Me), 26.00, 26.19, 26.96, and 27.60 (t, 4 CH_2), 27.65 (q, NMe), 32.32 (t, CH_2), 37.15 (d, C-2′), 38.93 (t, C-3′), 39.27 (d, ring CH), 54.40 and 58.94 (d, C-5, -4), 116.65 (t, C-5′), 136.04 (d, C-4′), 156.25 (s, C-2), 176.67 (s, C-1′). – MS (70 eV), m/z (%): 292 (1) [M^+], 195 (4), 113 (100). – $C_{17}H_{28}N_2O_2$ (292.2): calcd. C 69.81, H 9.66, N 9.58; found C 70.11, H 9.78, N 9.45.

(4R,5S,2′S)-4-Cyclohexyl-1,5-dimethyl-3-(2-methyl-3-oxo-3-phenylpropanoyl)imidazolidin-2-one (**30**): The lithium enolate of **9** (1.00 g, 3.97 mmol) was allowed to react with benzoyl chloride (0.46 ml, 3.97 mmol) according to General Procedure 3 to yield 1.23 g (87%) of **30** as white crystals, m. p. 111°C ($CHCl_3$/hexane), $[\alpha]_D^{25}$ = +40.0 (c = 1.35 in $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 2960 cm^{-1} (Me), 1732 (CO), 1696 (CO), 1676 (CO). – ^{1}H NMR ($CDCl_3$): δ = 1.00–1.90 (m, 11H, *c*-C_6H_{11}), 1.31 (d, 3H, J = 7 Hz, 5-Me), 1.41 (d, 3H, J = 7 Hz, 2′-Me), 2.72 (s, 3H, NMe), 3.70 (dq, 1H, J_a = J_b = 7 Hz, 5-H), 4.39 (dd, 1H, J = 2, 7 Hz, 4-H), 5.55 (q, 1H, J = 7 Hz, 2′-H), 7.41–7.58 (m, 3H, Ph), 8.00–8.07 (m, 2H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 12.84 (q, 5-Me), 13.68 (q, 2′-Me), 26.07, 26.12, 27.10, 27.27, and 32.16 (t, 5 CH_2), 27.52 (q, NMe), 39.90 (d, ring CH), 48.25 (d, C-2′), 54.58 and 59.23 (d, C-5, -4), 128.64, 132.74, and 135.93 (d, Ph), 156.27 (s, C-2), 170.22 (s, C-1′), 197.91 (s, C-3′). – MS (70 eV), m/z (%): 356 (4) [M^+], 251 (9), 223 (14), 195 (9), 113 (100). – $C_{21}H_{28}N_2O_3$ (356.2): calcd. C 70.74, H 7.92, N 7.86; found C 71.11, H 8.19, N 7.58.

(4R,5S,2′S)-4-Cyclohexyl-1,5-dimethyl-3-(2-methyl-3-oxobutanoyl)imidazolidin-2-one (**31**): The lithium enolate of **9** (1.00 g, 3.97 mmol) was allowed to react with acetyl chloride (0.28 ml, 3.97 mmol) according to General Procedure 3 to yield 0.93 g (80%) of **31** as colourless crystals, m. p. 93°C ($CHCl_3$/hexane), $[\alpha]_D^{25}$ = +54.00 (c = 1.80 in $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 2940 cm^{-1} (CH_2), 1728 (CO), 1716 (CO), 1688 (CO). – ^{1}H NMR ($CDCl_3$): δ = 1.05–1.82 (m, 11H, *c*-C_6H_{11}), 1.34 (d, 3H, J = 6.5 Hz, 2′-Me), 1.35 (d, 3H, J = 7 Hz, 5-Me), 2.33 (s, 3H, 4′-H), 2.75 (s, 3H, NMe), 3.72 (dq, 1H, J_a = J_b = 7 Hz, 5-H), 4.36 (dd, 1H, J = 2, 7 Hz, 4-H), 4.56 (q, 1H, J = 6.5 Hz, 2′-H). – ^{13}C NMR ($CDCl_3$): δ = 12.58 (q, 5-Me), 12.88 (q, 2′-Me), 26.15, 27.12 and 27.28 (t, 4 CH_2), 27.45 (q, NMe), 28.37 (q, C-4′), 32.28 (t, CH_2), 39.86 (d, ring CH), 53.04 (d, C-2′), 54.70 and 59.28 (d, C-5, -4), 156.36 (s, C-2), 169.62 (s, C-1′), 205.75 (s, C-3′). – MS (70 eV), m/z (%): 294 (0.8) [M^+], 252 (2), 223 (10), 113 (100). – $C_{16}H_{26}N_2O_3$ (294.2): calcd. C 65.26, H 8.91, N 9.52; found C 65.17, H 9.24, N 9.35.

(4R,5S,2′S)-4-Cyclohexyl-1,5-dimethyl-3-(2-methyl-3-oxopentanoyl)imidazolidin-2-one (**32**): The lithium enolate of **9** (0.50 g, 1.98 mmol) was allowed to react with propionic anhydride (0.26 ml, 1.98 mmol) according to General Procedure 3 to yield 0.52 g (85%) of **32** as white crystals, m. p. 83°C ($CHCl_3$/hexane), $[\alpha]_D^{25}$ = +19.46 (c = 2.23 in $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 2940 cm^{-1} (CH_2), 1731 (CO), 1709 (CO), 1690 (CO). – ^{1}H NMR ($CDCl_3$): δ = 1.10 (t, 3H, J = 7 Hz, 5′-H), 1.33 (2 d, 6H, J = 7 Hz, 5-Me and 2′-Me), 1.00–1.80 (m, 11H, *c*-C_6H_{11}), 2.67 (m, 2H, 4′-H), 2.74 (s, 3H, NMe), 3.70 (dq, 1H, J_a = J_b = 7 Hz, 5-H), 4.35 (dd, 1H, J = 2.4, 7 Hz, 4-H), 4.58 (q, 1H, J = 7 Hz, 2′-H). – ^{13}C NMR ($CDCl_3$): δ = 7.85 (q, C-5′), 12.93 (q, 5-Me), 12.99 (q, 2′-Me), 26.19, 27.11, 27.36, 32.34, and 33.96 (d, 5 ring CH_2 and C-4′), 27.52 (q, NMe), 39.78 (d, ring CH), 52.37 (d, C-2′), 54.73 and 59.32 (d, C-5, -4), 156.36 (s, C-2), 169.95 (s, C-1′), 208.18 (s, C-3′). – MS (70 eV), m/z (%): 308 (0.7) [M^+], 223 (18), 195 (3), 113 (100). – $C_{17}H_{28}N_2O_3$ (308.2): Calcd. C 66.67, H 9.15, N 9.15; found C 66.66, H 9.25, N 9.13.

(4R,5S,2'R)-4-Cyclohexyl-1,5-dimethyl-3-[(2-phenylseleno)butanoyl]imidazolidin-2-one (**33**): The lithium enolate of **11** (1.00 g, 3.76 mmol) and phenylselenyl chloride (0.72 g, 3.76 mmol) were allowed to react according to General Procedure 3. Purification by flash chromatography [diethyl ether/hexane (3:7)] yielded 1.05 g (66%) of **33** as a yellow oil, $[\alpha]_D^{25} = -23.25$ ($c = 7.44$ in $CHCl_3$). – IR (neat): $\tilde{\nu} = 2940\ cm^{-1}$ (CH_2), 1728 (CO), 1680 (CO). – ^1H NMR ($CDCl_3$): $\delta = 0.92$ (t, 3H, $J = 7$ Hz, 4'-H), 1.05–1.95 (m, 13H, *c*-C_6H_{11} and 3'-H), 1.33 (d, 3H, $J = 7$ Hz, 5-Me), 2.78 (s, 3H, NMe), 3.69 (dq, 1H, $J_a = J_b = 7$ Hz, 5-H), 4.39 (dd, 1H, $J = 2.5$, 7 Hz, 4-H), 5.11 (t, 1H, $J = 7.5$ Hz, 2'-H), 7.22–7.32 (m, 3H, Ph), 7.58–7.70 (m, 2H, Ph). – ^{13}C NMR ($CDCl_3$): $\delta = 12.62$ (q, C-4'), 13.11 (q, 5-Me), 24.19, 26.19, 27.08, 27.45, and 32.18 (t, 5 ring CH_2 and C-3'), 27.72 (q, NMe) 39.76 (d, ring CH), 42.61 (d, C-2'), 54.53 and 58.93 (d, C-5, -4), 128.03 and 128.75 (d, Ph), 135.73 (s, Ph), 156.22 (s, C-2), 172.54 (s, C-1'). – MS (70 eV), *m/z* (%): 422 (2) [M^+], 265 (37), 113 (100). – $C_{21}H_{30}N_2O_2Se$: calcd. 422.1472; found 422.1480 (MS).

General Procedure 4: Methanolysis of the Initial Aldol Products: Sodium metal (2.00 equiv.) was added to dry MeOH (4 ml) at 0°C and the mixture stirred for 30 min at room temp. under N_2. The reaction mixture was cooled to 0°C, then charged with a solution of the initial aldol (1.00 equiv.) in dry MeOH (2 ml), and stirred at 0°C for 3 h. Then the reaction was quenched with satd. aq. NH_4Cl. After removal of MeOH the aqueous phase was exhaustively extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$), concentrated, and purified by flash chromatography [diethyl ether/hexane (1:1)].

(2R,3R)-Methyl 3-Hydroxy-2-methyl-3-phenylpropanoate (**34**): Methanolysis of **13** or **24** (0.50 g, 1.42 mmol) according to General Procedure 4 afforded 206 mg (75%) of **34** as an oil, $[\alpha]_D^{25} = +23.30$ ($c = 1.00$ in $CHCl_3$) {ref.[2] $[\alpha]_D = +23.20$ ($c = 3.20$ in $CHCl_3$)}. – IR ($CHCl_3$): $\tilde{\nu} = 3450\ cm^{-1}$ (OH), 1734 (CO). – ^1H NMR ($CDCl_3$): $\delta = 1.24$ (d, 3H, $J = 7$ Hz, 2-Me), 2.78 (dq, 1H, $J = 7$, 4.3 Hz, 2-H), 3.11 (br s, 1H, OH, D_2O exch.), 3.64 (s, 3H, OMe), 5.07 (d, 1H, $J = 4.3$ Hz, 3-H), 7.24–7.35 (m, 5H, Ph). – ^{13}C NMR ($CDCl_3$): $\delta = 10.78$ (q, 2-Me), 46.45 (d, C-2), 51.87 (q, OMe), 73.66 (d, C-3), 125.95, 127.48, and 128.24 (d, Ph), 141.47 (s, Ph), 176.14 (s, C-1). – MS (70 eV), *m/z* (%): 194 (49) [M^+], 107 (98), 88 (100). – $C_{11}H_{14}O_3$ (194.1): calcd. C 68.02, H 7.26; found C 68.32, H 7.11.

(2R,3R)-Methyl 3-Hydroxy-2-methyl-3-(4-nitrophenyl)propanoate (**35**): Methanolysis of **14** (0.50 g, 1.26 mmol) according to General Procedure 4 afforded 240 mg (80%) of **35** as a yellow oil, $[\alpha]_D^{25} = +14.30$ ($c = 1.30$ in $CHCl_3$). – IR (neat): $\tilde{\nu} = 3500\ cm^{-1}$ (OH), 1730 (CO), 1605 (Ph), 1350 (NO_2). – ^1H NMR ($CDCl_3$): $\delta = 1.09$ (d, 3H, $J = 7$ Hz, 2-Me), 2.81 (dq, 1H, $J = 7$, 4 Hz, 2-H), 3.10–3.45 (br s, 1H, OH, D_2O exch.), 3.72 (s, 3H, OMe), 5.25 (d, 1H, $J = 4$ Hz, 3-H), 7.51–8.22 (m, 4H, Ar). – ^{13}C NMR ($CDCl_3$): $\delta = 10.34$ (q, 2-Me), 45.94 (d, C-2), 52.22 (q, OMe), 72.59 (d, C-3), 123.50 and 126.90 (d, Ar), 147.24 and 148.92 (s, Ar), 175.87 (s, C-1). – MS (70 eV), *m/z* (%): 239 (5) [M^+], 208 (5), 152 (33), 88 (100). – $C_{11}H_{13}NO_5$ (239.1): calcd. C 55.23, H 5.48, N 5.85; found C 55.54, H 5.48, N 5.63.

(2R,3R)-Methyl 3-Hydroxy-3-(4-methoxyphenyl)-2-methylpropanoate (**36**): Methanolysis of **15** (0.50 g, 1.30 mmol) according to General Procedure 4 afforded 220 mg (75%) of **36** as a yellow oil, $[\alpha]_D^{25} = +16.90$ ($c = 0.13$ in $CHCl_3$). – IR (neat): $\tilde{\nu} = 3500\ cm^{-1}$ (OH), 1732 (CO), 1612, 1508 (Ph). – ^1H NMR ($CDCl_3$): $\delta = 1.14$ (d, 3H, $J = 7$ Hz, 2-Me), 2.75 (dq, 1H, $J = 7$, 5 Hz, 2-H), 3.08 (br s, 1H, OH, D_2O exch.), 3.63 (s, 3H, 1-OMe), 3.78 (s, 3H, Ar-OMe), 4.98 (d, 1H, $J = 5$ Hz, 3-H), 6.83–6.88 and 7.21–7.27 (m, 4H, Ar). – ^{13}C NMR ($CDCl_3$): $\delta = 11.22$ (q, 2-Me), 46.70 (d, C-2), 51.82 (q, 1-OMe), 55.21 (q, Ar-OMe), 73.57 (d, C-3), 113.60 and 127.18 (d, Ar), 133.72 and 158.91 (s, Ar), 176.07 (s, C-1). – MS (70 eV), *m/z* (%): 224 (11) [M^+], 193 (2), 137 (100). – $C_{12}H_{16}O_4$ (224.1): calcd. C 64.27, H 7.19; found C 63.99, H 7.49.

(2R,3S)-Methyl 3-Hydroxy-2-methylbutanoate (**37**): Methanolysis of **21** (0.40 g, 1.35 mmol) according to General Procedure 4 afforded 125 mg (70%) of **37** as a colourless oil, $[\alpha]_D^{25} = -13.42$ ($c = 0.514$ in MeOH) {ref.[3] $[\alpha]_D = -13.50$ ($c = 0.867$ in MeOH)}. – IR (neat): $\tilde{\nu} = 3500\ cm^{-1}$ (OH), 2980 (Me), 1760 (CO). – ^1H NMR ($CDCl_3$): $\delta = 1.18$ (d, 3H, $J = 6$ Hz, 4-H), 1.20 (d, 3H, $J = 7$ Hz, 2-Me), 2.53 (dq, 1H, $J = 7$, 4 Hz, 2-H), 2.73 (br s, 1H, OH), 3.72 (s, 3H, OMe), 4.08 (dq, 1H, $J = 6$, 4 Hz, 3-H). – ^{13}C NMR ($CDCl_3$): $\delta = 11.13$ (q, 2-Me), 19.88 (q, C-4), 45.62 (d, C-2), 51.96 (q, OMe), 68.22 (d, C-3), 176.40 (s, C-1). – MS (70 eV), *m/z* (%): 132 (1) [M^+], 101 (15), 88 (100).

(2R,3S)-Methyl 3-Hydroxy-2,4-dimethylpentanoate (**38**): Methanolysis of **22** (0.40 g, 1.23 mmol) according to General Procedure 4 yielded 134 mg (68%) of **38** as a colourless oil, $[\alpha]_D^{25} = +7.63$ ($c = 1.205$ in $CHCl_3$) {ref.[2] $[\alpha]_D = +7.70$ ($c = 5.40$ in $CHCl_3$)}. – IR (neat): $\tilde{\nu} = 3465\ cm^{-1}$ (OH), 2960 (Me), 1760 (CO). – ^1H NMR ($CDCl_3$): $\delta = 0.88$ (d, 3H, $J = 7$ Hz, 4-Me), 1.00 (d, 3H, $J = 7$ Hz, 5-H), 1.18 (d, 3H, $J = 7$ Hz, 2-Me), 1.68 (2 dq, 1H, $J = 8$, 7 Hz, 4-H), 2.68 (dq, 1H, $J = 7$, 4 Hz, 2-H), 2.63–2.78 (br s, 1H, OH), 3.57 (dd, 1H, $J = 4$, 8 Hz, 3-H), 3.71 (s, 3H, OMe). – ^{13}C NMR ($CDCl_3$): $\delta = 10.29$ (q, 2-Me), 18.63 (q, 4-Me), 19.18 (q, C-5), 30.77, (d, C-4), 41.99 (d, C-2), 51.99 (q, OMe), 77.07 (d, C-3), 176.98 (s, C-1). – MS (70 eV), *m/z* (%): 160 (9) [M^+], 117 (62), 88 (100). – $C_8H_{16}O_3$: calcd. 160.1099; found 160.1088 (MS).

(2R,3S)-Methyl 3-Cyclohexyl-3-hydroxy-2-methylpropanoate (**39**): Methanolysis of **23** (0.50 g, 1.37 mmol) according to General Procedure 4 yielded 214 mg (78%) of **39** as a yellow oil, $[\alpha]_D^{25} = -6.17$ ($c = 1.103$ in CH_2Cl_2). – IR (neat): $\tilde{\nu} = 3500\ cm^{-1}$ (OH), 2930 (CH_2), 1760 (CO). – ^1H NMR ($CDCl_3$): $\delta = 0.85–1.85$ (m, 10H, *c*-C_6H_{11}), 1.17 (d, 3H, $J = 7$ Hz, 2-Me), 2.00–2.15 (m, 1H, ring CH), 2.50–2.65 (br s, 1H, OH), 2.68 (dq, 1H, $J = 7$, 3.3 Hz, 2-H), 3.64 (dd, 1H, $J = 3.3$, 8.5 Hz, 3-H), 3.71 (s, 3H, OMe). – ^{13}C-NMR ($CDCl_3$): $\delta = 9.92$ (q, 2-Me), 25.86, 26.07, 26.33, 28.99, and 29.13 (t, CH_2), 40.06 (d, ring CH), 41.15 (d, C-2), 51.86 (q, OMe), 75.71 (d, C-3), 177.14 (s, C-1). – MS (70 eV), *m/z* (%): 200 (1) [M^+], 182 (2), 117 (43), 88 (100). – $C_{11}H_{20}O_3$: calcd. 200.1412; found 200.1408 (MS).

General Procedure 5: Reductive Cleavage of **27** *and* **28**: A solution of the appropriate substrate (1.00 equiv.) in dry THF (10 ml) was added to a stirred suspension of $LiAlH_4$ (2.50 equiv.) in THF (5 ml) at 0°C. After 3 h at 0°C the reaction was quenched with satd. aq. NH_4Cl, then extracted with Et_2O. The combined extracts were dried ($MgSO_4$), concentrated, and purified.

(S)-2-Methyl-3-phenylpropan-1-ol (**40**): Applying General Procedure 5 to **27** (0.40 g, 1.17 mmol) afforded 131 mg (75%) of **40** as a colourless oil after purification by flash chromatography [diethyl ether/hexane (3:7)], $[\alpha]_D^{25} = -11.02$ ($c = 2.75$ in C_6H_6 {ref.[25] $[\alpha]_D = -11.08$ ($c = 4.60$ in C_6H_6)}. – IR (neat): $\tilde{\nu} = 3380\ cm^{-1}$ (OH), 2940 (CH_2), 1608 (Ph). – ^1H NMR ($CDCl_3$): $\delta = 0.86$ (d, 3H, $J = 7$ Hz, 2-Me), 1.89 (m, 1H, 2-H), 2.34 (dd, 1H, $J = 5$, 13 Hz, 3-H), 2.74 (dd, 1H, $J = 6$, 13 Hz, 3-H), 2.98 (br s, 1H, OH), 3.38 (dd, 1H, $J = 6$, 11 Hz, 1-H), 3.46 (dd, 1H, $J = 6$, 11 Hz, 1-H), 7.18–7.30 (m, 5H, Ph). – ^{13}C NMR ($CDCl_3$): $\delta = 16.43$ (q, 2-Me), 37.81 (d, C-2), 39.74, (t, C-3), 67.52 (t, C-1), 125.77, 128.17, and 129.11 (d, Ph), 140.66 (s, Ph). – MS (70 eV), *m/z* (%): 150 (22) [M^+], 132 (16), 117 (57), 91 (100). – $C_{10}H_{14}O$: calcd. 150.1045; found 150.1044 (MS).

(S)-2-Methyldecan-1-ol (**41**): Applying General Procedure 5 to **28** (0.50 g, 1.37 mmol) afforded 170 mg (72%) of **41** as a colourless oil after purification by flash chromatography [diethyl ether/hexane (1:1)], $[\alpha]_D^{25} = -9.94$ ($c = 3.00$ in CH_2Cl_2) {ref.[26] $[\alpha]_D = -10.00$ ($c = 4.20$ in CH_2Cl_2)}. – IR (neat): $\tilde{\nu} = 3360$ cm^{-1} (OH), 2940 (CH_2). – ^1H NMR ($CDCl_3$): $\delta = 0.88$ (t, 3H, $J = 6.5$ Hz, 10-H), 0.91 (d, 3H, $J = 7$ Hz, 2-Me), 1.00–1.50 (m, 14H, 7 CH_2), 1.60 (m, 1H, 2-H), 2.28 (br s, 1H, OH), 3.43 (dd, 1H, $J = 6$, 11 Hz, 1-H), 3.46 (dd, 1H, $J = 6$, 11 Hz, 1-H). – ^{13}C NMR ($CDCl_3$): $\delta = 14.18$ (q, C-10), 16.67 (q, 2-Me), 22.79, 27.12, 29.48, 29.76, 30.11, 32.05, and 33.32 (t, 7 CH_2), 35.88 (d, C-2), 68.53 (t, C-1). – MS (70 eV), *m/z* (%): 154 (4) [$M^+ - 18$], 69 (35), 57 (80), 43 (100). – $C_{11}H_{24}O$: calcd. 172.1827; found 172.1824 (MS).

(S)-Benzyl 2-Methylpent-4-enoate (**42**): To a cold (–78°C) solution of benzyl alcohol (0.53 ml, 5.13 mmol) in dry THF (15 ml), was added *n*-BuLi (1.90 ml of a 1.80 M solution in cyclohexane, 3.42 mmol). After 30 min at this temp. the reaction mixture was charged with a cooled (–78°C) solution of **29** (0.50 g, 1.71 mmol) in THF (5 ml). The reaction mixture was stirred at –50°C for 3 h, then aq. pH 7 phosphate buffer was added. The resultant mixture was partitioned between H_2O and CH_2Cl_2. The organic extracts were combined, dried ($MgSO_4$), concentrated and purified by flash chromatography [diethyl ether/hexane (3:7)] to afford 314 mg (90%) of **42** as a colourless oil, $[\alpha]_D^{25} = +0.94$ ($c = 2.45$ in $CHCl_3$). – IR (neat): $\tilde{\nu} = 2980$ cm^{-1} (Me), 1740 (CO), 1648 (C=C), 1452 (Ph). – ^1H NMR ($CDCl_3$): $\delta = 1.16$ (d, 3H, $J = 7$ Hz, 2-Me), 2.17 (m, 1H, 3-H), 2.42 (m, 1H, 3-H), 2.56 (tq, 1H, $J_a = J_b = 7$ Hz, 2-H), 5.02 (m, 2H, 5-H), 5.09 (s, 2H, CH_2O), 5.70 (m, 1H, 4-H), 7.27–7.34 (m, 5H, Ph). – ^1H NMR ($CDCl_3$): $\delta = 16.50$ (q, 2-Me), 37.77 (t, C-3), 39.21 (d, C-2), 66.03 (t, CH_2O), 116.91 (t, C-5), 128.08 128.48, and 135.33 (d, Ph), 136.18 (s, Ph), 175.67 (s, C-1). – MS (70 eV), *m/z* (%): 204 (2) [M^+], 91 (100), 41 (30). – $C_{13}H_{16}O_2$: calcd. 204.1150; found 204.1161 (MS).

(S)-4-Methyl-1,5-diphenyl-3-(phenylethynyl)pent-1-yn-3-ol (**43**): To a cold (–78°C) stirred solution of phenylacetylene (0.26 ml, 2.37 mmol) in dry THF (10 ml) was added *n*BuLi (1.30 ml of a 1.80 M solution in cyclohexane, 2.34 mmol) dropwise under nitrogen. After 30 min the reaction mixture was added to a precooled (–78°C) solution of **27** (0.80 g, 2.34 mmol) in THF (10 ml) by rapid cannulation. The reaction mixture was stirred for a further 30 min at –78°C, then satd. aq. NH_4Cl (10 ml) was added and the mixture extracted with Et_2O (3 × 20 ml). The combined extracts were dried ($MgSO_4$), concentrated and purified by flash chromatography [diethyl ether/hexane (1:9)] to afford 344 mg (42% based on **27**) of **43** as a brown oil, $[\alpha]_D^{25} = -1.67$ ($c = 8.32$ in $CHCl_3$). – IR (neat): $\tilde{\nu} = 3440$ cm^{-1} (OH), 3040 (Ph), 2240 (C≡C), 1604 (Ph). – ^1H NMR ($CDCl_3$): $\delta = 1.18$ (d, 3H, $J = 6$ Hz, 4-Me), 2.40 (m, 1H, 4-H), 2.57 (dd, 1H, $J = 11$, 13 Hz, 5-H), 3.16 (s, 1H, OH), 3.53 (dd, 1H, $J = 2$, 13 Hz, 5-H), 7.12–7.52 (m, 15H, 3 Ph). – ^{13}C NMR ($CDCl_3$): $\delta = 14.25$ (q, 4-Me), 38.10 (t, C-5), 47.27 (d, C-4), 68.32 (s, C-3), 84.48, 84.62, 88.55, and 88.65 (s, 2 C≡C), 122.10 (s, Ph), 125.89, 128.24, 128.64, 129.28, and 131.81 (d, Ph), 140.71 (s, Ph). – MS (70 eV), *m/z* (%): 332 (1) [$M^+ - 18$], 129 (100), 102 (74). – $C_{26}H_{22}O$: calcd. 350.1670; found 350.1680.

(S)-3-Butyl-2-methyl-1-phenylheptan-3-ol (**44**): To a cold (–78°C) stirred solution of **27** (0.40 g, 1.17 mmol) in dry THF (10 ml) was added dropwise under nitrogen *n*BuLi (0.65 ml of a 1.80 M solution in cyclohexane, 1.17 mmol). After 30 min at –78°C the reaction was quenched with satd. aq. NH_4Cl (5 ml) and the mixture extracted with Et_2O (3 × 10 ml). The combined extracts were dried ($MgSO_4$), concentrated, and purified by flash chromatography [diethyl ether/hexane (3:7)] to afford 122 mg (40% based on **27**) of **44** as a colourless oil, $[\alpha]_D^{25} = -8.13$ ($c = 0.123$ in $CHCl_3$). – IR (neat): $\tilde{\nu} = 3382$ cm^{-1} (OH), 2940 (CH_2), 1498 (Ph). – ^1H NMR ($CDCl_3$): $\delta = 0.77$ (d, 3H, $J = 7$ Hz, 2-Me), 0.80–1.70 (m, 19H, 6 CH_2, 2 Me and OH), 1.86 (m, 1H, 2-H), 2.18 (dd, 1H, $J = 11$, 13 Hz, 1-H), 3.01 (dd, 1H, $J = 2.6$, 13 Hz, 1-H), 7.12–7.32 (m, 5H, Ph). – ^{13}C NMR ($CDCl_3$): $\delta = 13.20$ (q, 2-Me), 14.19 (q, C-4′ and C-7), 23.48, 23.52, 25.38, 25.52, 36.07, 36.28, and 37.19 (t, 7 CH_2), 42.37 (d, C-2), 76.05 (s, C-3), 125.63, 128.19 and 129.17 (d, Ph), 142.15 (s, Ph). – MS (70 eV), *m/z* (%): 204 (17) [$M^+ - 57$], 187 (4), 91 (100). – $C_{18}H_{30}O$ (262.2): calcd. C 82.37, H 11.53; found C 82.45, H 11.27.

(S)-1-(1,3-Dithian-2-yl)-3-methyl-4-phenylbutan-2-one (**45**): To a cold (–30°C) stirred solution of 1,3-dithiane (0.30 g, 2.50 mmol) in dry THF (10 ml) was added *n*BuLi (1.30 ml of a 1.80 M solution in cyclohexane, 2.34 mmol) dropwise under nitrogen. After 1.5 h the reaction mixture was added to a cooled (–30°C) solution of **27** (0.80 g, 2.34 mmol) in THF (10 ml) by rapid cannulation. This reaction mixture was stirred for a further 30 min at –30°C, then allowed to warm to –5°C over 1 h. The reaction was quenched with satd. aq. NH_4Cl (10 ml) and the mixture extracted with Et_2O (3 × 20 ml). The combined extracts were washed successively with aq. $Na_2S_2O_5$ (3%), aq. KOH (5%), and H_2O. The extracts were dried ($MgSO_4$), concentrated, and purified by flash chromatography [diethyl ether/hexane (1:9)] to afford 0.40 g (64%) of **45** as a colourless oil, $[\alpha]_D^{25} = +123.23$ ($c = 3.28$ in $CHCl_3$). – IR (neat): $\tilde{\nu} = 2960$ cm^{-1} (CH_2), 1712 (CO), 1456 (Ph). – ^1H NMR ($CDCl_3$): $\delta = 1.15$ (d, 3H, $J = 7$ Hz, 3-Me), 1.95 (m, 2H, CH_2), 2.45 (m, 1H, 3-H), 2.65 (dd, 1H, $J = 7$, 13 Hz, 4-H), 2.95 (dd, 1H, $J = 7$, 13 Hz, 4-H), 3.12 (m, 4H, 2 SCH_2), 3.92 (s, 1H, 1-H), 7.14–7.30 (m, 5H, Ph). – ^{13}C NMR ($CDCl_3$): $\delta = 17.49$ (q, 3-Me), 25.09 (t, CH_2), 25.74 and 25.86 (t, 2 SCH_2), 40.01 (t, C-4), 46.05 and 46.45 (d, C-1 and -3), 126.30, 128.33, and 128.92 (d, Ph), 139.18 (s, Ph), 204.89 (s, C-2). – MS (70 eV), *m/z* (%): 266 (3) [M^+], 119 (100), 91 (33). – $C_{14}H_{18}OS_2$: calcd. 266.0799; found 266.0792 (MS).

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