Asymmetric Diels–Alder Reactions. A Route to Chiral Carbocycles *via* Bicyclic Lactams†‡

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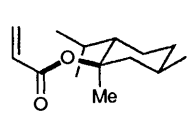
The L-valinol-derived unsaturated lactam methyl 3-isopropyl-7a-methyl-5-oxo-2,3-dihydro-7a*H*-pyrrolo[2,1-*b*]oxazole-6-carboxylate functions as an excellent chiral dienophile in asymmetric Diels–Alder reactions. Diene approach occurs exclusively from the α-(*endo*) face to provide optically pure tricyclic lactams. In the presence of Lewis acids, increases in rate, regiospecificity, and 'Alder *endo*' stereoselectivity are observed. Elaboration of the cycloadducts provided an unexpected entry into cyclopropane-containing polycyclic systems *via* an *N*-acyliminium ion-enamide rearrangement. In addition, a number of optically pure carbocycles were readily prepared *via* this methodology.

The Diels–Alder reaction must be ranked among the most powerful transformations in organic chemistry. In addition to forming two new sigma bonds, the potential exists for the formation of four contiguous stereocentres. For these reasons, the asymmetric Diels–Alder reaction has attracted considerable interest. The bulk of previous asymmetric Diels–Alder reactions have utilized chiral dienophiles,[1] although both chiral dienes[2] and chiral Lewis acid catalysts[3] have also been employed. The earliest chiral dienophile was utilized by Walborsky[4] which involved the menthyl acrylate **1**, while some years later Corey[5] employed the pulegone-derived acrylate **2**. More recently



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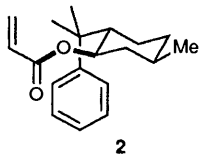

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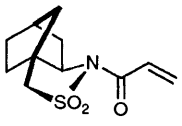
Oppolzer[6] described reaction of the sultam **3**, Masamune[7] the *tert*-butyl enone **4**, and Evans[8] employed the oxazolidinone **5**, all serving as efficient chiral dienophiles to effect Diels–Alder reactions. We now describe, in some detail,† our studies in-



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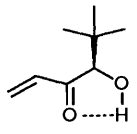

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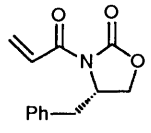
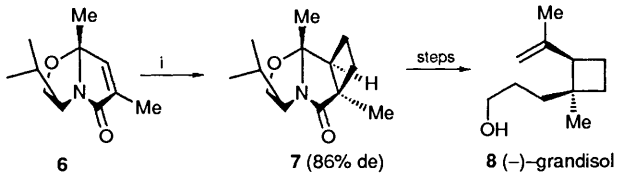


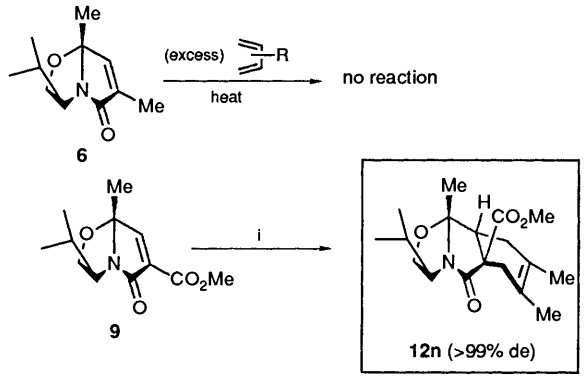
5

volving the readily available chiral bicyclic lactam **9** as a useful partner in these cycloadditions. Chiral bicyclic lactams have already served as valuable templates in reaching a variety of chiral quaternary carbon compounds. Their original application in asymmetric alkylations[9] has now been extended to include asymmetric [2 + 2] photocycloadditions[10] and [2 + 1] cycloadditions[11] with unsaturated substrates such as **6** and **9**, furnishing important products such as **8** and **11** *via* the respective intermediates **7** and **10**. In an effort to extend their versatility to include the synthetically important [4 + 2] cycloadditions, thermal reactions of lactam **6** with various dienes were first examined. No reactivity was observed, even after prolonged heating. However, use of the more reactive dieno-



Reagents and conditions: i, CH_2Cl_2, *hv*; ii, CH_2=S(O)Me

phile **9** with 2,3-dimethylbuta-1,3-diene led to tricyclic adduct **12n** in 89% yield. The diastereoselectivity was established *via* X-ray crystal-structure determination of the corresponding *tert*-



Reagent: i, CH_2=CMeCMe=CH_2

butyl ester **13** (Fig. 1) and the presence of a 4–5% nuclear Overhauser enhancement (NOE) between the angular methyl group and the adjacent proton (11-H)§ in adducts **12n** and **13**. Most importantly, adduct **12n** *and all other* [4 + 2] *cycloaddition products from dienophile* **9** *were formed as single diastereoisomers.* No evidence [NMR, HPLC, or capillary column GLC (VPC)] for the product of entry from the α-(*endo*) face (*i.e.* **12x**) has ever been observed. The cycloaddition furnishing adduct **12n** in excellent yield was originally performed by simple

† Submitted to mark the 150th anniversary of the Chemical Society/Royal Society of Chemistry.

‡ For a preliminary account of this work, see: A. I. Meyers and C. A. Busacca, *Tetrahedron Lett.*, 1989, **30**, (*a*) 6973; (*b*) 6977.

§ Crystallographic, non-systematic numbering scheme.

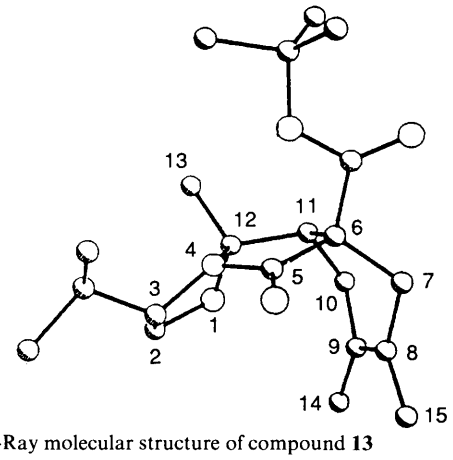
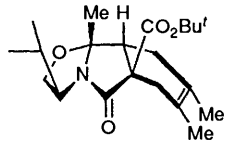


Fig. 1 X-Ray molecular structure of compound **13**



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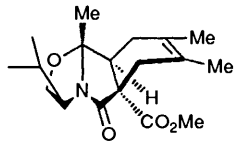
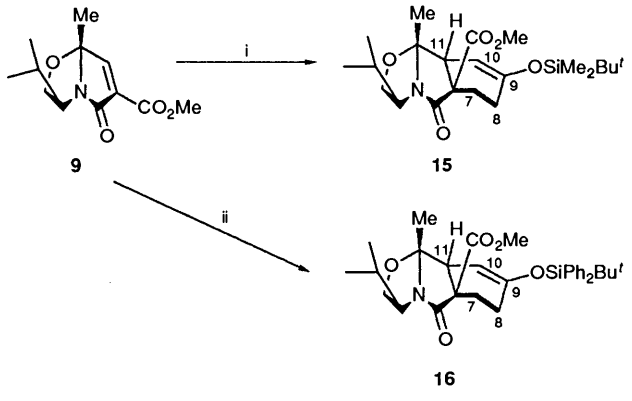


12x

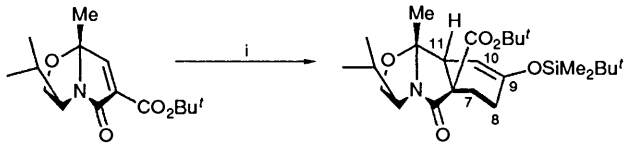
dissolution of lactam **9** in excess of 2,3-dimethylbuta-1,3-diene and warming of the solution for 8 h at 60 °C. It was subsequently found that similar results may be achieved in 48 h at ambient temperature. The siloxy dienes[12] **14a** and **14b** also proved to be excellent partners in this thermal process, producing tricyclic systems **15** and **16** in 89 and 100% yield,



9 **15** **16**

Reagents: i, CH_2=CHC(OSiMe$_2$Bu^t)=CH_2 (**14a**), 89%; ii, CH_2=CHC(OSiPh$_2$Bu^t)=CH_2 (**14b**), 100%

respectively. Once again the cycloadducts were obtained as single stereo- and regio-isomers. The observed regiocontrol was not entirely unanticipated, as 2-oxygenated dienes are known[13] to provide higher regioselectivities due to perturbation of the diene HOMO. The *tert*-butyl ester **17** was found to behave similarly, providing the tricycle **18a** in 89% yield. Furthermore, it was found that chromatography of these cycloadducts on silica gel induced *complete* double-bond isomerization from the initial $\Delta^{8,9}$ position to the $\Delta^{9,10}$ site. This easy isomerization was only observed in the adducts possessing an oxygen substituent at C-9. This was readily confirmed by ^{1}H NMR spectroscopy wherein 11-H appears as a very distinct doublet of doublets (dd), with coupling constants of 4 and 7 Hz, resonating at $\delta \sim 3$. In cycloadducts **15**, **16** and **18a**, all possessing an oxy substituent at C-9, proton decoupling easily reveals a single 4-proton spin system (7α-, 7β-, 8α- and 8β-H) and a single 2-proton spin system (10- and 11-H) in the cyclohexene moiety. The 11-H signals appear as broadened singlets which sharpen distinctly upon irradiation of vinyl protons 10-H. Further experimental evidence of double-bond isomerization in *alkyl*-

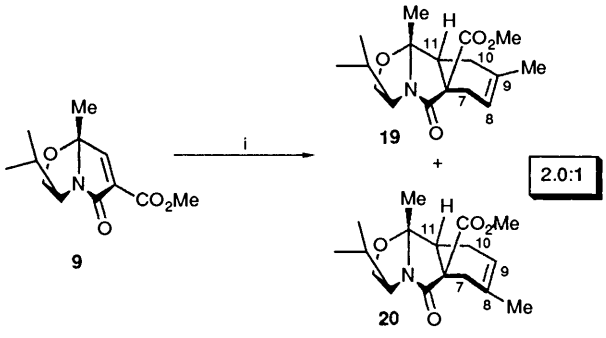


17 **18a**

Reagent: i, **14a**, 89%

substituted cycloadducts was also gathered (*vide infra*). These observations were made during the course of (i) *palladium*-catalysed hydrogenations of various tricyclic lactams, and (ii) cycloadditions catalysed by strong Lewis acids. Although molecular models provide no real insight as to the reason for this phenomenon, a large increase in the thermodynamic stability of the $\Delta^{9,10}$ silyl enol ethers must prevail in these systems.

When lactam **9** was dissolved in isoprene (20 mol equiv.), sealed in a thick-walled glass bomb, and heated for 18 h at 60 °C, the regioisomeric cycloadducts **19** and **20** were obtained as a chromatographically inseparable 2.0:1 mixture in 74% yield. Poor regioselectivity in isoprene cycloadditions has been encountered earlier[14] by several groups and the problem has

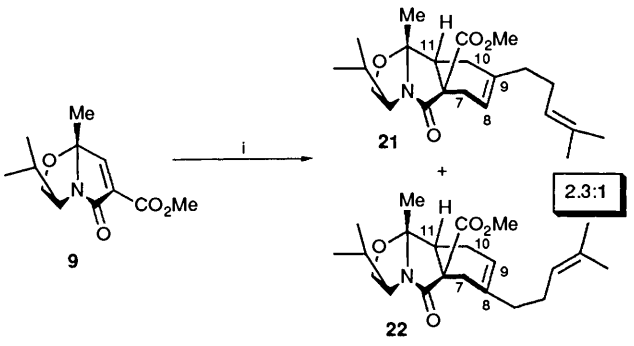


9 **19** **20**

Reagent and conditions: i, CH_2=CHCMe=CH_2 (excess), 60 °C, 74%

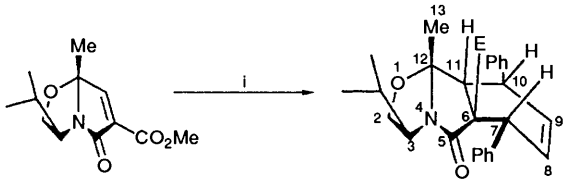
occasionally endured even after Lewis acid catalysts were employed, necessitating the preparation and use of isoprene equivalents such as 2-(phenylthiomethyl)buta-1,3-diene. Excellent resolution of the ^{1}H NMR spectrum of the mixture **19** + **20** allowed complete proton-decoupling experiments on the mixture to be performed. The possibility that one of the components was a double-bond isomer as seen in the silyl enol ethers was readily ruled out as the signal for 11-H exists as a clear doublet of doublets for both components. Irradiation of vinyl 8-H in isomer **9** produced precise collapse of the 7-H doublet of doublets to a simple doublet, while irradiation of vinyl 9-H in isomer **20** led to perturbation of the complex signal for 10-H. In the final analysis, the cyclohexane portion of major component **19** was found to comprise two 3-proton spin systems: 11-, 10α-, 10β-H and 8-, 7α-, 7β-H. Conversely, minor component **20** possessed one 4-proton spin system (11-, 10α-, 10β-, 9-H) and one 2-proton spin system (7α-, 7β-H). These results are fully consistent with the proposed regiochemical assignments for isomers **19** and **20**.

Utilization of the common diene myrcene under thermal conditions furnished the tricyclic adducts **21** and **22** as a 2.3:1 mixture of regioisomers in 70% yield. The results of the ^{1}H NMR decoupling experiments on the mixture **21** + **22** were



Reagent and conditions: i, CH_2=CHC(=CH_2)CH_2CH_2CH=CMe_2 (excess), 70°

completely analogous to those performed on the isoprene cycloadducts (**19**, **20**) and thus the structural assignments appear to be correct. Two additional dienes, cyclohexa-1,3-diene and 2,5-dimethylfuran, were treated with lactam **9** and produced no cycloadduct after prolonged heating. This, however, did not come as a complete surprise, since furans and pyrroles are known[15] to be poor dienes for Diels–Alder reactions. The lack of reactivity of cyclohexa-1,3-diene was, however, somewhat perplexing. The low propensity for cycloaddition in this case may stem in part from the creation of a fairly hindered transition state *via* the constrainment of the ethano bridge. Continuing the search for additional dienes of increasing complexity, we treated 1,4-diphenylbuta-1,3-diene (5 mol equiv.) with lactam **9** in toluene (0.1 mol dm^{-3} soln) and crystalline tricyclic lactam **23** was obtained *as a single diastereoisomer* in 86% yield. This result provided an opportunity to assess

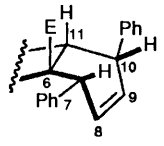


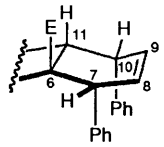
Reagent: i, PhCH=CHCH=CHPh, 86%

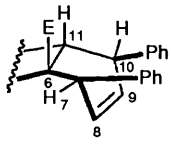
potential control of stereocentres C-7 and C-10 ('Alder *endo*' selectivity), as 1,4-disubstituted butadienes necessarily create four contiguous stereocentres upon cycloaddition. The fact that a single product was obtained was deemed rather significant. Assuming complete facial selectivity, two different diastereoisomeric cycloadducts could have been formed, furnishing either the α-diphenyl (**A**,**B**) or β-diphenyl adducts (**C**,**D**). In addition to this, two different boat conformations were considered likely for each diastereoisomer. A homonuclear NOE experiment on compound **23** was first performed. The expected facial selectivity (*endo*) was verified as irradiation of the angular methyl C-13 singlet provided a 7% NOE of the adjacent 11-H doublet. Irradiation of 11-H, however, led to no enhancement of the transannular proton, 7-H and the question of secondary stereoselectivity remained unanswered. Complete ^{1}H assignments for tricycle **23** were achieved *via* routine decoupling of all resonances. A summary of the decoupling results is shown in Table 1. An examination of entry 2 of Table 1 provides some appreciation of the complexity of the cyclohexene spin system in lactam **23**. Irradiation of 10-H causes simplification of every proton in the spin system as noted from the splitting patterns of

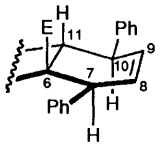
Table 1 Summary of ^{1}H decoupling experiments on lactam **23**

Entry	Irradiation frequency (δ/ppm)	Result
1	3.35 (11-H)	10-H simplifies
2	3.75 (10-H)	7-, 8-, 9-, 11-H simplify
3	5.80 (9-H)	7-, 8-, 10-H simplify
4	5.89 (8-H)	7-, 9-, 10-H simplify
5	4.22 (7-H)	8-, 9-, 10-H simplify

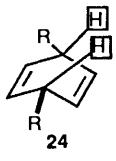

A α–diphenyl


B α–diphenyl


C β–diphenyl


D β–diphenyl

7-, 8-, 9 and 11-H. This demonstrates that not only were the required vicinal (^3J) couplings of 10-H to 11-H and 9-H present, but also ^4J (10-H–8-H) and ^5J (10-H–7-H) long-range couplings. Proton 11-H is a doublet with J 8.6 Hz resonating at δ 3.35. The magnitude of J for 11-H was of paramount importance. In conformation **A**, the vicinal Karplus angle between 11-H and 10-H is ~40°, suggesting a ^3J range of 6–10 Hz.[16] In conformation **D**, this angle is very nearly 180°, suggesting a maximal coupling[16] in the 10–14 Hz range. The observed magnitude of the coupling strongly disfavours conformation **D**. Proton 10-H gives rise to a complex multiplet resonating at δ 3.75 which is partly overlapped by the oxazolidine 3-H signal. Four lines were distinguishable and the three coupling constants J 2.8, 5.8, 8.6 Hz were found. The 8.6 Hz coupling was clearly $J_{10,11}$. The 2.8 Hz coupling appears to be $J_{10,9}$ since 9-H was found to be a doublet of triplets with J 2.5, 10.0 Hz, the latter coupling clearly being $J_{9,8}$. The most important 10-H coupling constant is J 5.8 Hz. This coupling constant seems most likely to be due to homoallylic (^5J) coupling between 10-H and 7-H. Large ^5J (π) coupling constants (5–11 Hz) have been previously observed[16] in systems such as **24** where both C–H bonds are parallel to the p-orbitals of the adjacent π-system. It is precisely this type of geometry which is present in conformation **A**.



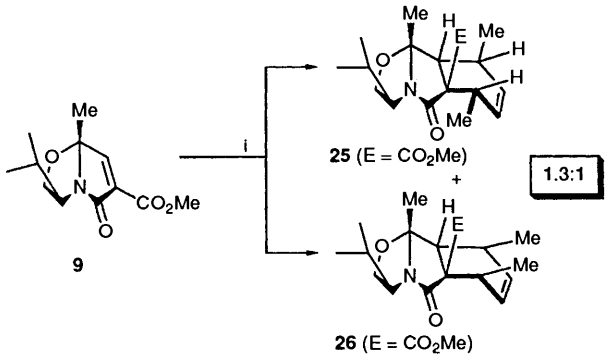
24 ^5J (π) 5.5–11Hz

Additional support for these assignments arises from the single-crystal X-ray structure of an analogous cycloadduct derived from a 1,4-disubstituted butadiene, *i.e.* adduct **25**, along with complete NMR assignments, and literature precedent for closely related compounds.

In this regard, thermal cycloaddition of lactam **9** with (*E*,*E*)-hexa-2,4-diene proceeded in 87% yield to furnish diastereoisomeric adducts **25** and **26** in a 1.3:1 ratio. Chromatography of this mixture provided the major component **25** as a crystalline material, which was subjected to X-ray crystal analysis (Fig. 2). Examination of this X-ray structure clearly reveals the boat conformation and a-disposition of the C-7 and C-10 methyl

Table 2 Comparison of ^{1}H NMR data for adducts **27a** and **25**

Signal	Description: Cycloadduct **27a** (Thomas) (δ, mult., J/Hz)	Description: Cycloadduct **25** (this work) (δ, mult., J/Hz)
15-Hz	1.30, d, 7.3	1.36 d, 7.3
14-Hz	1.50, d, 7.3	1.43, d, 6.8
11-H	3.22, d, 5.0	2.68, d, 5.9
10-H	2.56, m	2.38, m
9-H	5.68, dt, 3.0, 9.0	5.45, dt, 3.5, 8.7
8-H	5.74, dt, 3.0, 9.0	5.73, dt, 3.5, 8.7
7-H	3.22, m	2.66, m



Reagent: i, MeCH=CHCH=CHMe (excess), 87%

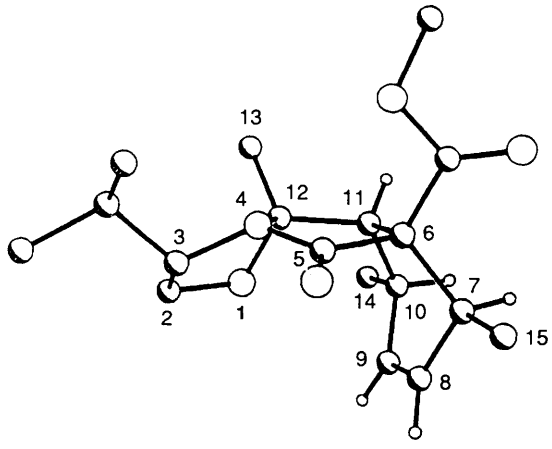
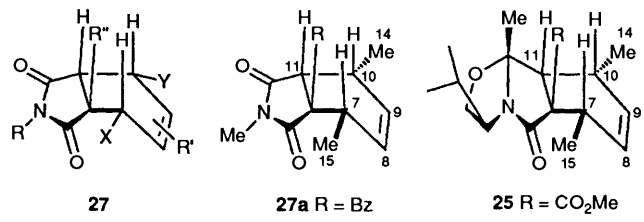
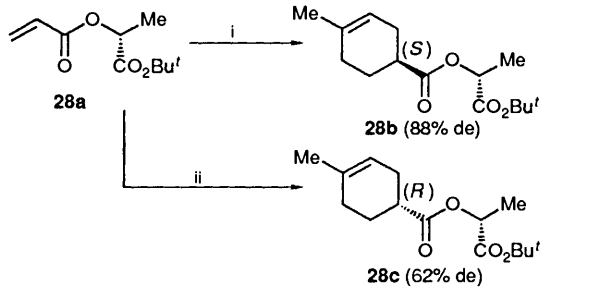


Fig. 2 X-Ray molecular structure of compound **25**

groups which occupy the requisite positions for the large ^5J couplings described above for compound **23**. Additional NMR experiments performed on lactam **25** suggested a close correlation between the solution conformation and solid-state structure. The 7-H–10-H ^5J coupling was clearly present, as were all of the spectroscopic features discussed for tricyclic lactam **23**. A further source of support for these assignments came from reported ^{1}H NMR data[17–21] for cycloadducts of general form **27**. Thomas' work on cytochalasins[19–21] includes a number of cycloadducts similar to those found in this work. Cytochalasin precursor **27a**, for example, shows a remarkably similar ^{1}H NMR spectrum to that of the tricyclic adduct **25**, as shown in Table 2.

Lewis Acid-catalysed Cycloadditions.—Attention was next turned to potential Lewis acid catalysis in these lactam cycloadditions since they have been used in Diels–Alder reactions to increase reaction rates,[22] regioselectivity,[23] π-facial selectivity[24] and 'Alder *endo*' selectivity.[25] Despite the potential for enhancing utility the use of Lewis acid catalysts may also present protracted problems; *e.g.*, sulphonamides **3** were reported[26] to be unstable towards strong Lewis acids, necessitating the use of weaker acids. This is also true of several other chiral auxiliaries derived from chiral alcohols.[27] Lewis acids may also promote polymerization of the diene used,[28] and other serious difficulties may also compete with the cycloaddition process. In a significant finding, Helmchen[29] reported that in the [4 + 2] cycloaddition of isoprene to dienophile **28a**, the π-facial selectivity could be *reversed* by changing the catalyst from $TiCl_4$ to $AlCl_2Et$. Since then, other groups[30] have made

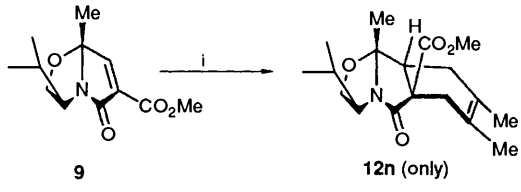




Reagents: i, CH_2=CHCMe=CH_2, $TiCl_4$; ii, CH_2=CHCMe=CH_2, $AlCl_2Et$

similar discoveries involving the reversal of facial selectivity. Mattay *et al.*,[31] in their work with chiral dioxolanones, found much *higher* selectivities under thermal conditions than when Lewis acids were employed. In most of these cases the observed facial selectivity could not be predicted beforehand. Therefore the use of Lewis acid catalysts, although interesting, is not always a valuable player in these processes.

Treatment of a solution of lactam **9** in excess of 2,3-dimethylbuta-1,3-diene with the weak Lewis acid $ZnCl_2$ led to the tricyclic lactam **12n** in 84% yield after 1 h at 25 °C. The observed rate increase of the catalysed reaction over the earlier described thermal process (48 h, 25 °C) is remarkable considering that the reaction mixture was heterogeneous. The tricyclic lactam **12n** was identical in all respects with that obtained from the un-



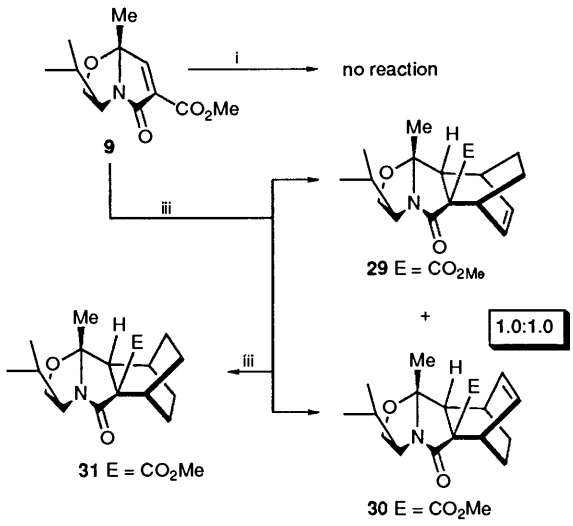
Reagents: i, CH_2=CMeCMe=CH_2 (excess), $ZnCl_2$, 84%

catalysed reaction. More importantly, no trace of any *exo*-cycloadduct **12x** could be detected. A variety of Lewis acid-catalysed cycloadditions were undertaken to evaluate reaction rates and yields under different conditions. The reaction of lactam **9** with 2,3-dimethylbuta-1,3-diene was examined first so that the potential complications of regiochemistry and secondary (Alder *endo*) stereochemistry could be avoided. These results, along with the previously performed non-catalysed cycloadditions, are presented in Table 3. Pronounced rate enhancements for the cycloadditions were consistently observed with Lewis acids. Even the heterogeneous reactions (entries 3 and 4), wherein $ZnCl_2$ was largely undissolved, exhibited pro-

found rate enhancement. The stronger Lewis acid $SnCl_4$ was found to be equally suitable (entries 5–7) provided that less than one molar equivalent of catalyst was used, and the reactions were performed at low temperature. Boron trifluoride–diethyl ether (entry 8) caused instant polymerization of the reaction mixture to a solid mass, thus precluding it from further study. It is noteworthy that adduct **12n** was the only product observed in each case, dispelling any further concern over loss of stereoselectivity. As a further demonstration of rate enhancement by use of Lewis acid catalysts, addition of cyclohexa-1,3-diene to lactam **9** was re-examined under $SnCl_4$ catalysis and the mixture was found to undergo cycloaddition in good yield at 20 °C to give diastereoisomeric cycloadducts **29** and **30** as a 1:1 mixture. While the lack of Alder *endo* selectivity was disappointing, entry into these systems which were inaccessible under thermal conditions was encouraging. These structural assignments and the relationship of adduct **29** to isomer **30** were verified by hydrogenation of the mixture to the single saturated product **31** in high yield.

The use of Lewis acids potentially to overcome the poor regiocontrol seen earlier in the case of isoprene and myrcene was now considered a worthwhile endeavour. The utilization of $ZnCl_2$ indeed caused a dramatic increase in regioselectivity even when the reaction was performed heterogeneously (Table 4). When the reaction was carried out in dichloromethane at 0 °C a very respectable 25:1 ratio of regioisomers **19:20** was realized. Similar success was observed in the catalysis of the myrcene cycloaddition. The regioisomeric ratio of products **21:22** was increased to 15.2:1 with $ZnCl_2$ in dichloromethane at 0 °C (Table 5).

Hence, dramatic regioselective effects were observed with $ZnCl_2$, which took a poorly selective cycloaddition process and transformed it into one of ready practicality. Attention was next focused on the possibility of increasing the secondary (Alder *endo*) stereoselectivity in the cycloadditions of lactam **9** with 1,4-disubstituted butadienes. The results obtained *via* Lewis acid catalysis are shown in Table 6. As seen from the data, *endo* selectivity was indeed increased *via* the use of Lewis acid



Reagents and conditions: i, cyclohexa-1,3-diene (excess), 48 h, reflux; ii, cyclohexa-1,3-diene (8 mol equiv.), CH_2Cl_2, $SnCl_4$ (0.2 mol equiv.), −20 °C, 75%; iii, H_2, Pd/C, 92%

catalysts. Use of weak Lewis acids (entries 3–6) caused only a moderate increase, however, to an upper limit of ~2.5:1 (**25:26**). Use of $SnCl_4$ in toluene at −60 °C (entry 7) increased the ratio to 7.0:1, yet some starting mterial remained, and gave rise to two unidentified products totalling 17% of the reaction mixture. The best selectivity was obtained (entry 8) using $SnCl_4$ at −60 °C. Unfortunately, 41% of the reaction mixture in this example was composed of the same two unidentified products observed in entry 7. The chromatographic complexity of the four-component mixture prevented full characterization of these substances although spectroscopic evidence suggested they were probably isomeric materials in the cyclohexene portion, generated under the influence of the strong Lewis acids. The possibility that these two products were diastereoisomers from β-cycloaddition appears unlikely considering the data acquired with the 2,3-dimethylbutadiene and cyclohexa-1,3-diene discussed earlier. Interestingly, these same two products were observed during the *palladium*-catalysed hydrogenation of the mixture **25** + **26**. These isomeric products were resistant to standard (50 psi) hydrogenation procedure, yet clearly possessed vinylic signals as seen in the ^1H NMR spectrum of these mixtures. Since palladium is known [32] to cause isomerization of olefins during hydrogenations, platinum (3% Pt/C) was utilized. The hydrogenation proceeded cleanly to give the saturated lactams **32** + **33** only.

Asymmetric Epoxidation.—The concave nature of the tricyclic adducts as observed *via* X-ray and NMR data suggested the potential for high β-face selectivity in additions to the cyclohexene double bond. Treatment of cycloadduct **12n** with *m*-chloroperbenzoic acid (MCPBA)–Na_2HPO_4 in dichloromethane at −27 °C gave a 9:1 mixture of β-epoxide **34** to α-

Table 3 Lewis acid-catalysed cycloadditions of lactam **9** with 2,3-dimethylbuta-1,3-diene

Entry	Conditions	Product, comments
1	excess of diene, neat, 8 h, 70 °C	**12n**, 89% yield
2	excess of diene, neat, 48 h, 25 °C	**12n**, 85% yield
3	8 mol equiv. diene, 1 mol equiv. $ZnCl_2$, heterogeneous, 16 h, −27 °C	**12n** 12%, **9** 75%
4	8 mol equiv. diene, 1 mol equiv. $ZnCl_2$, heterogeneous, 1 h, 25 °C	**12n**, 84% yield
5	8 mol equiv. diene, CH_2Cl_2, 0.1 mol equiv. $SnCl_4$, 1.5 h, −65 °C	**12n** 76%, **9** 24%
6	8 mol equiv. diene, 0.2 mole equiv. $SnCl_4$, homogeneous, 1 h, −45 °C	**12n** 75%, **9** 19%
7	8 mol equiv. diene, CH_2Cl_2, 0.2 mol equiv. $SnCl_4$, 2 h, −55 °C	**12n**, 84% yield
8	8 mol equiv. diene, 0.05 mol equiv., BF_3·Et_2O, 25 °C	polmerization

Table 4 Effect of added $ZnCl_2$ on the regioselectivity of the reaction of lactam **9** with isoprene

Entry	Conditions	Products	Ratio
1	excess of isoprene, sealed tube, 24 h, 60 °C, 74% yield	**19** + **20**	2.0:1
2	8 mol equiv. isoprene, 1 mol equiv. $ZnCl_2$, heterogeneous, 1 h, 25 °C, 85% yield	**19** + **20**	12.5:1
3	10 mol equiv. isoprene, 1 mol equiv. $ZnCl_2$, homogeneous CH_2Cl_2, 4 h, 0 °C, 71% yield	**19** + **20**	25.0:1

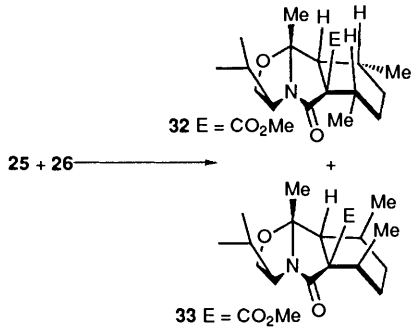
Table 5 Effect of added $ZnCl_2$ on regioselectivity of lactam **9** with myrcene

Entry	Conditions	Products	Ratio
1	excess of myrcene, neat 18 h, 75 °C, 70% yield	**21** + **22**	2.3:1
2	8 mol equiv. myrcene 1 mol equiv. $ZnCl_2$, heterogeneous, 4 h, 25 °C, 68% yield	**21** + **22**	7.3:1
3	10 mol equiv. myrcene, 1 mol equiv. $ZnCl_2$, CH_2Cl_2, 36 h, 0 °C, 66% yield	**21** + **22**	15.2:1

Table 6 Effect of added Lewis acids on the *endo*/*exo* selectivity of the reaction of lactam **9** with (*E*,*E*)-hexa-2,4-diene

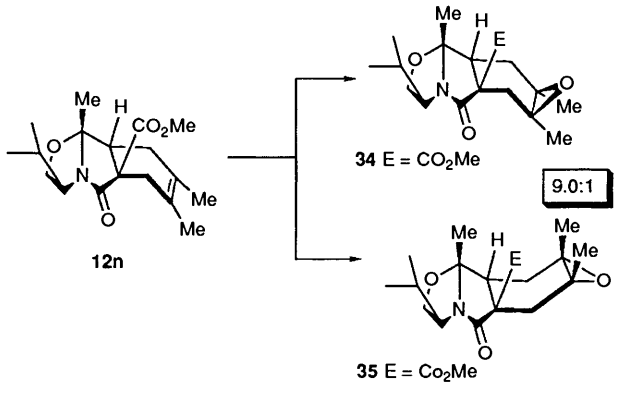
Entry	Conditions	Products, comments	Ratio determined by capillary GC
1	excess of diene, neat, 24 h, 25 °C	**25** + **26** 51% y, 36% s.m.	1.3:1
2	excess of diene, neat, 8 h, 70 °C	**25** + **26** 87% yield	1.3:1
3	8 mol equiv. diene, water + CH_2Cl_2, 1 mol equiv. $ZnCl_2$, 48 h, 25 °C	**25** + **26** 30% y, 57% s.m.	1.4:1
4	8 mol equiv. diene, CH_2Cl_2, 0.2 mol equiv. LiBr, 24 h, 25 °C	**25** + **26** 23% y, 62% s.m.	1.8:1
5	8 mol equiv. diene, neat, 1 mol equiv. LiBr, 24 h, 25 °C	**25** + **26** 87% yield	2.2:1
6	8 mol equiv. diene, CH_2Cl_2, 0.2 mol equiv. $ZnCl_2$, 24 h, 0 °C	**25** + **26** 87% yield	2.5:1
7	8 mol equiv. diene, PhMe, 0.2 mol equiv. $SnCl_4$, 24 h, −60 °C then 0 °C	**25** + **26** + X[b] 53% y, 23% s.m., 17% X	7.0:1
8	8 mol equiv. diene, CH_2Cl_2, 0.2 mol equiv. $SnCl_4$, 4 h, −60 °C	**25** + **26** + X[b] 55% yield, 41% X	10.0:1

[a] y = yield, s.m. = starting material. [b] See text.



Reagents: i, H_2, 3% Pt/C

epoxide **35**. Chromatography of this mixture (see Experimental section) permitted separation and characterization of the major



and minor epoxides. The results of NOE experiments on epoxides **34** and **35** (Tables 7 and 8) provided clear-cut

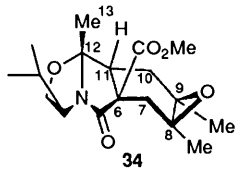


Table 7 NOE Results on major epoxide **34**

Entry	Proton irradiated	Proton enhanced, % NOE[a]
1	11-H	13-H_3, 4.4%; 10β-H, 5.3%
2	15-H_3	10α-H, 0.9%; 10β-H, 1.1%
3	14-H_3	7α-H, 0.5%; 7β-H, 1.6%

[a] Non-deoxygenated samples.

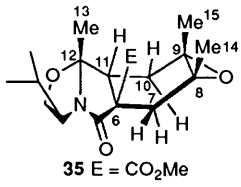


Table 8 NOE Results on minor epoxide **35**

Entry	Proton irradiated	Proton enhanced, % NOE[a]
1	14-H_3 + 15-H_3 (singlet)	11-H, 8.9%; 7β-H, 0.8%; 10β-H, 0.5%; 7α-H, 0.3%
2	11-H	13-H_3 + 10α-H, 11%; 10β-H, 2.0%

[a] Non-deoxygenated samples.

stereochemical assignment regarding the facial selectivity of the epoxidation. From the NOE data obtained from the minor epoxide **35**, an 8.9% NOE enhancement of 11-H was observed following irradiation of the 14-H_3 + 15-H_3 singlet (Table 8).

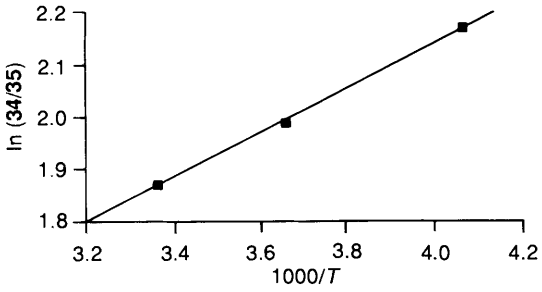
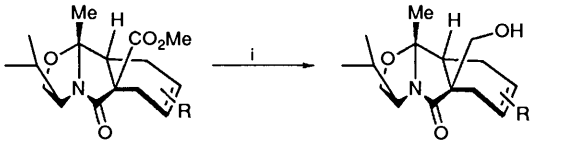


Fig. 3 Asymmetric epoxidation as a function of temperature

This clearly established the expected β-face approach of the peracid to tricyclic lactam **12n**. The assymmetric epoxidation was repeated at several temperatures and a plot of ln (**34**/**35**) *vs.* $1/T$ is shown in Fig. 3. The linear correlation was excellent and suggested a ratio of ~12:1 (90% de) would be expected at −100 °C, although reaction times would likely be in the order of several days. No attempts at improvement in epoxidation stereoselectivity using bulkier oxidizing agents or different substrates were attempted, yet the potential for use of these optically pure Diels–Alder adducts *themselves* as chiral templates was demonstrated.

With the cycloaddition process well established, attention was turned to conversion of the carboxylic ester of the tricyclic lactams into a methyl substituent, and subsequent removal of the chiral auxiliary leading to carbocycles with an angular methyl substituent. After considering different reducing agents and conditions, ethanolic $NaBH_4$ was found to be optimum for this transformation, affording alcohols **36** in good yield. While normally a slow reducing system for esters,[33] $NaBH_4$–EtOH proved to be a mild and high-yield method for generation of the

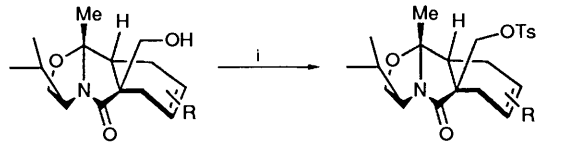


12 n R = 8, 9–diMe
19 R = 9–Me
21 R = 9–$CH_2CH_2CH{=}CMe_2$

36 a R = 8, 9–diMe
36 b R = 9–Me
36 c R = 9–$CH_2CH_2CH{=}CMe_2$

Reagents and conditions: i, $NaBH_4$, EtOH, 24 h, 25 °C, >90%

alcohol without any concomitant lactam reduction. In nearly all cases saturated NH_4Cl proved to be a suitable quench for this reduction, yet in one case (reduction of myrcene cycloadduct **21**) a stable borate was formed which required

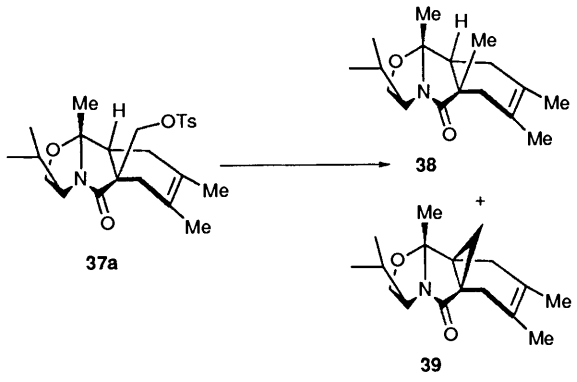


36 a R = 8, 9–diMe
36 b R = 9–Me
36 c R = 9–$CH_2CH_2CH{=}CMe_2$

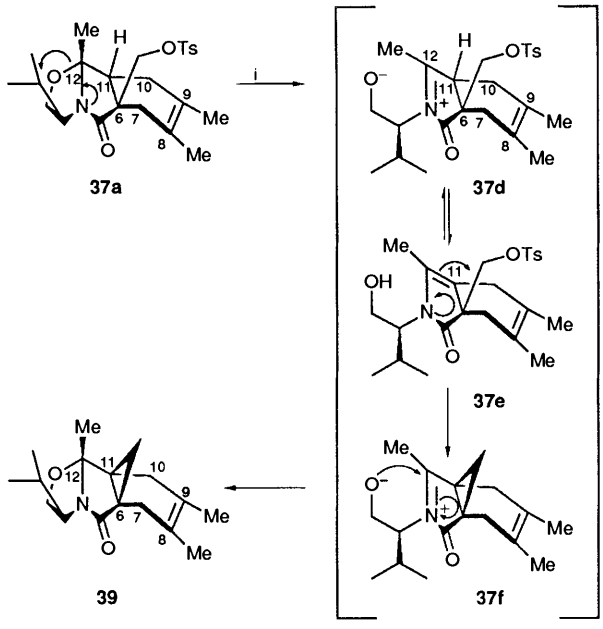
37 a R = 8, 9–diMe
37 b R = 9–Me
37 c R = 9–$CH_2CH_2CH{=}CMe_2$

Reagents: i, TsCl, DMAP, 90–99%

glacial HOAc for hydrolysis. Tosylation of these neopentyl alcohols with tosyl chloride under basic conditions proceeded in excellent yield to give compounds **37** and transformation of the tosate group to the methyl group was expected to be routine. This was, however, *not* the case as treatment of tosyl ester **37a** with $NaBH_4$–Me_2SO (DMSO) gave a complex mixture of products, including both the desired methyl compound **38** and the unexpected cyclopropane **39**. In an attempt to access the



underlying cause for the unusual generation of the cyclopropane **39**, the experiment was repeated with omission of the reducing agent. The sole product obtained in >99% yield was the cyclopropyl species **39**. This remarkable transformation, which probably involves an *N*-acyliminium ion-enamide tautomer, **34** is outlined in Scheme 1. The ring-chain

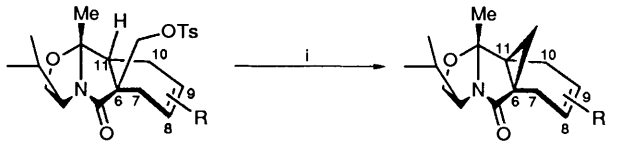


Scheme 1 *Conditions:* i, heat, DMSO

tautomerism, present in species **37a**, may be considered to give rise to the acyliminium intermediate **37d** which can exist in an equilibrium involving the rearranged partner **37e**. The latter is suitably set to undergo an intramolecular alkylation to furnish the cyclopropane **37f**. This sequence of events then leaves the acyliminium ion with a tethered nucleophile, *i.e.* **37f**, which is capable of returning to the ring-closed system **39**. Support for this as a general reaction sequence was gathered by an analogous system behaving in a similar fashion.[34]

The cyclopropanes **40** and **41** were prepared in this fashion in very high overall yield. In addition, siloxy cycloadduct **18b** was converted into keto cyclopropane **46** *via* the sequence depicted with the intermediacy of species **43** and **45**. In the final step of this sequence (**45** to **46**) the released TsOH served efficiently to hydrolyse the ketal moiety.

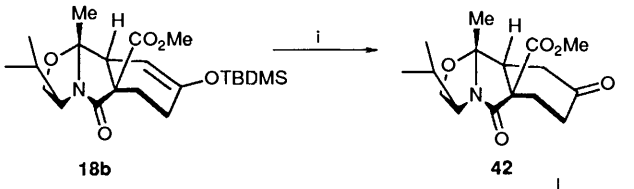
To demonstrate the potential for construction of optically pure carbocycles *via* this methodology, the cyclopropane **39** was subjected to a three-step sequence. Treatment of compound **39** with n-butyllithium at −27 °C led to enamine **47**, which was subjected to immediate acid hydrolysis to furnish diketone **48** in 98% yield over two steps. Base-catalysed aldol cyclization of this



37a; R = 8, 9-diMe
b; R = 9-Me
c; R = $CH_2CH_2CH{=}CMe_2$

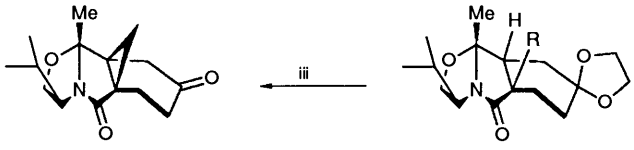
39 R = 8, 9-diMe
40 R = 9-Me
41 R = $CH_2CH_2CH{=}CMe_2$

Conditions: i, heat, DMSO



18b

42

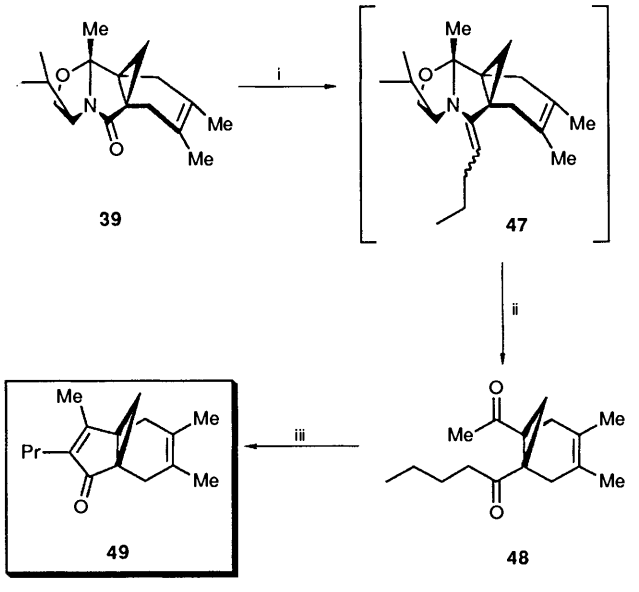


46

43 R = CO_2Me
44 R = CH_2OH
45 R = CH_2OTs

Reagents and conditions: i, Bu_4NF; ii, $HO[CH_2]_2OH$; iii, heat, DMSO

material furnished the optically pure [4.3.1.0] system **49** in 91% yield. The observed regiocontrol in the final aldol closure may well be due to the greater thermodynamic stability of the butyl enolate over the less highly substituted methyl enolate. Our



39

47

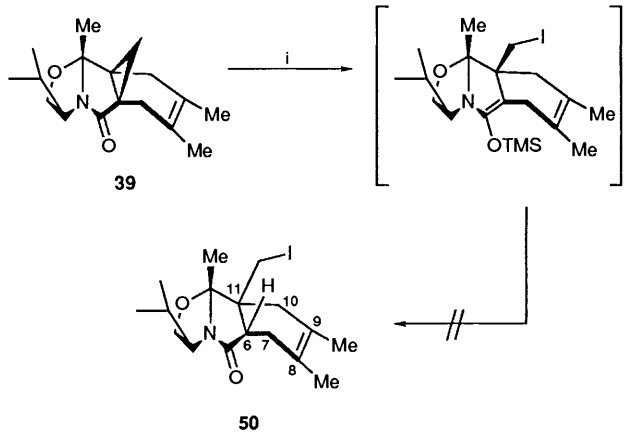
49

48

Reagents: i, BuLi; ii, H^+, 98%; iii, NaOEt, 91%

earlier plan to transform the ester to a methyl group was again addressed. In this instance it was felt that the latter could be obtained by reduction of the cyclopropane. The cyclopropane **39**, however, proved highly resistant toward hydrogenation under a wide array of catalysts and conditions.

Based on literature precedent,[35] iodotrimethylsilane (TMSI) was examined and the 11-iodomethyl species **50** was expected to be formed. In the event, treatment of compound **39** with TMSI at −27 °C gave only clean conversion into the 6-iodomethyl

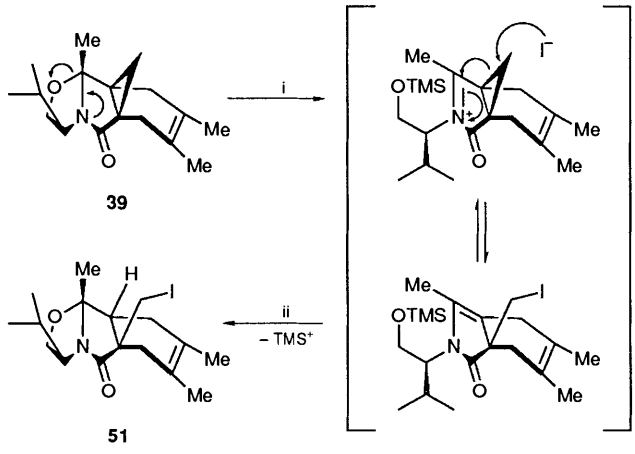


39

50

Reagent: i, TMSI

compound **51**. Once again, readily occurring *N*-acyliminium ion formation dictated the regiochemistry of cyclopropane-ring opening. This reaction was found to be general, as cyclopropanes **40** and **41** also underwent this transformation in



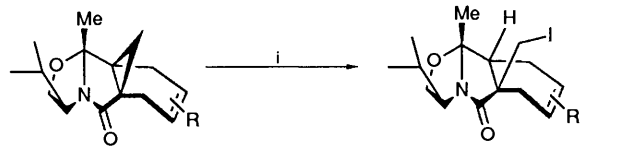
39

51

Reagents: i, TMSI; ii, water

nearly quantitative yield and with complete regiocontrol to furnish iodides **52** and **53**, respectively.

The approach to the methyl group now required transformation of the iodide to the hydride. Reduction of the neopentyl iodide **51** with $NaBH_4$ in DMSO was shown to be



40 R = 9-Me
41 R = 9-$CH_2CH_2CH{=}CMe_2$

52 R = 9-Me
53 R = 9-$CH_2CH_2CH{=}CMe_2$

Reagent: i, TMSI

unsatisfactory, resulting in variable yields of the methyl lactam **38**. A general method for the reduction of these neopentyl iodides was found through the use of the recently reported[36] magnesium in methanol reduction, originally developed for aryl halides. Treatment of the iodides **51**–**53** with 4 molar equivalents of magnesium powder in MeOH at ambient temperature led to 59–62% chromatographed yields of methyl species **38**, **54** and **55**. These reductions were found to proceed equally well on all scales attempted and NMR analyses of all methyl compounds were fully consistent with the stated

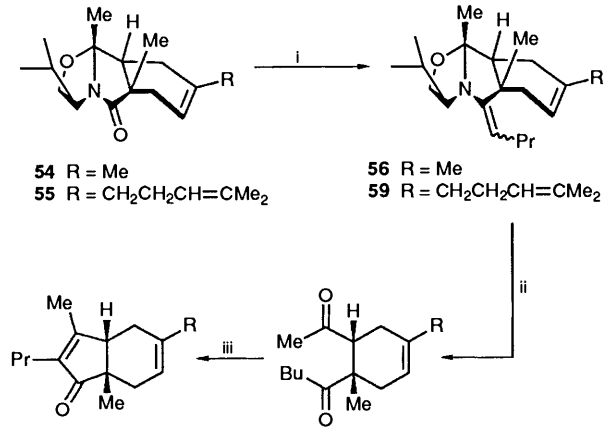
regiochemistry for cyclopropane ring-opening discussed above. Routine homonuclear decoupling experiments and simple examination of proton multiplicities on tricyclic lactam **54**, for example, revealed two 3-proton spin systems (11-, 10α-, 10β-H and 7α-, 7β-, 8-H) for the cyclohexene ring. The isomeric 6-methyl species would have possessed one 4-proton and one 2-

51 R = 8, 9–diMe
52 R = 9–Me
53 R = 9–$CH_2CH_2CH{=}CMe_2$

38 R = 8, 9–diMe
54 R = 9–Me
55 R = 9–$CH_2CH_2CH{=}CMe_2$

Reagents: Mg^0, MeOH 59–62%

proton spin system for this same structural moiety. The stage was now set for removal of the chiral auxiliary and acquisition of several representative functionalized, optically pure carbocyclic systems. Isoprene-derived tricyclic lactam **54** was treated with three molecular equivalents of butyllithium at −27 °C to give crude enamine **56**, which was immediately hydrolysed with 1 mol dm^{-3} $Bu_4NH_2PO_4$ to give diketone **57**. Aldol cyclization then furnished carbocycle **58** in 55% overall yield. Again, two aldol products from dione **57** could have been formed, yet in the cyclization only a single regioisomer was



54 R = Me
55 R = $CH_2CH_2CH{=}CMe_2$

56 R = Me
59 R = $CH_2CH_2CH{=}CMe_2$

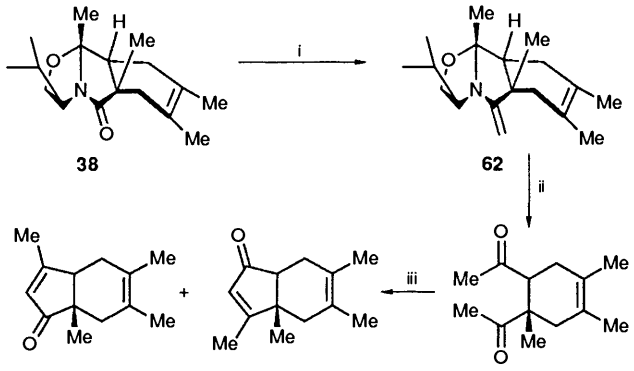
58 R = Me
61 R = $CH_2CH_2CH{=}CMe_2$

57 R = Me
60 R = $CH_2CH_2CH{=}CMe_2$

Reagents and conditions: i, BuLi (3 mol equiv.), −27 °C; ii, H^+; iii, NaOEt (55–61% overall)

obtained. This result is likely due to both increased thermodynamic stability of the butyl enolate and disfavoured attack of the methyl ketone enolate on the adjacent neopentyl carbonyl. Myrcene-derived lactam **55** was similarly treated with butyllithium at −27 °C to yield enamine **59**, which readily underwent acid hydrolysis to give diketone **60**. The sequence was again completed *via* catalysed aldol cyclization to furnish target molecule **61** in 61% overall yield.

Several additional examples of enantiomerically pure carbocycles were examined, when tricyclic lactam **38** was treated with three molecular equivalents of methyllithium at −27 °C to give crude enamine **62**, and after acid hydrolysis provided diketone **63**. As expected, little regiocontrol was observed in the final aldol closure, and a 1.3:1 mixture (GLC) of carbocycles **64** and **65** was obtained in 35% overall yield. Isomeric carbocycles **64** and **65** proved to be inseparable by chromatography.

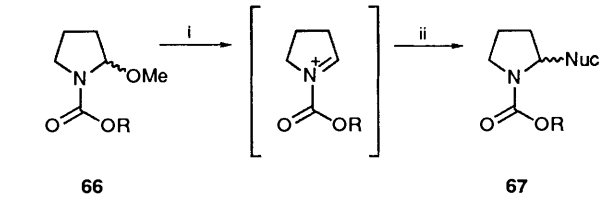


38 **62** **64** **65** **63**

Reagents and conditions: i, MeLi (3 mol equiv.), −27 °C; ii, H^+; iii, NaOEt, 35%

Mechanistic aspects.—(a) *Steric factors.* Bicyclic lactam **9** is a rigid 5-membered-ring dienophile whose high facial selectivity observed in Diels–Alder cycloadditions may be steric in origin, arising from blockage of the β-face by the angular methyl and/or isopropyl groups. Although plausible, several factors argue against this explanation. First, each X-ray structure of bicyclic and tricyclic lactams obtained to date as well as NOE data show the isopropyl group to be equatorial and truly remote from the reactive centres. In addition, the angular methyl group (C-13) always appears to be bent back slightly from the A ring. In short, the angular methyl substituent no doubt causes some hindrance to approach from the top face, yet its molecular volume appears to be insufficient to account for the *complete* facial selectivity observed in these systems.

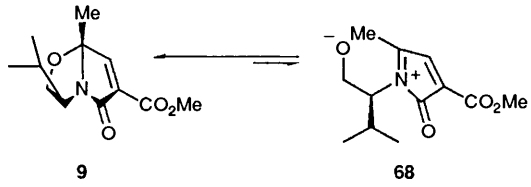
(b) *N-Acyliminium intermediates.* Carbamates such as **66** extensively studied by Speckamp[37] have been shown to react with weak Lewis acids such as $ZnCl_2$ to give acyliminium intermediates, which were readily trapped with nucleophiles to give species **67**. The identical conditions utilized by Speckamp



66 **67**

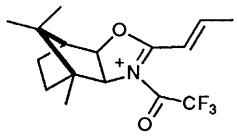
Reagents: i, $ZnCl_2$; ii, Nuc

($ZnCl_2$ in dichloromethane) were employed in a large number of the Lewis acid-catalysed cycloadditions discussed in the present study. This fact, coupled with the ample evidence for reversible acyliminium formation in these bicyclic and tricyclic lactams which has already been presented, suggests the potential involvement of a species such as **68** in these cycloadditons.



9 **68**

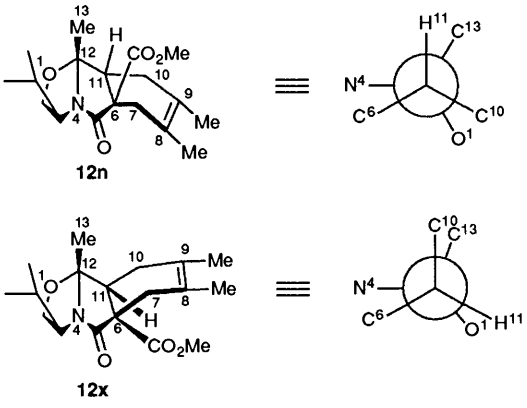
Several antiaromatic species such as **68** have been postulated to explain transformations within the pyrrole literature.[38–41] Furthermore, chiral *N*-acyliminium species **69** has been used[42] as a dienophile in asymmetric Diels–Alder reactions. Circumstantial evidence therefore exists for the presence of low concentrations of



69

zwitterion, **68** in the thermal and certainly the Lewis acid-catalysed cycloadditions of unsaturated bicyclic lactams. In the absence of additional information, however, the role of zwitterion **68** in determining facial selectivity remains uncertain.

Torsional Angles.—It is tempting to invoke the torsional angle arguments of Houk[43] and others[44] to explain the facial selectivity in these reactions. While olefinic carbon C-7 of substrate **9** does not appear to be significantly pyramidalized, an examination of the two possible cycloadducts, for example **12n** (*endo*) and **12x** (*exo*), is more suggestive. Newman projections of **12n** (observed) and **12x** (not observed) about the C-11–C-12 bond are depicted below. In compound **12n**, the C-11–H-11 and C-12–C-13 bonds are staggered, as are the C-11–C-10 and



12n

12x

C-12–O-1 bonds. In contrast, significant eclipsing of these same bonds are noted for **12x**. Preliminary molecular modelling results* show *endo* cycloadduct **12n** to be approximately 2.5 kcal mol^{-1} † lower in energy than *exo* adduct **12x**. Therefore, if a late transition state exists for these transformations, *endo* attack may predominate in order to avoid these two unfavourable eclipsing interactions. It is clear from the previous discussion that the underlying cause of the selectivity is still an open question. What is interesting, however, is the possibility of several minor (or weak) factors being responsible.

Conclusions.—Unsaturated bicyclic lactam **9** has been developed as an excellent chiral dienophile for asymmetric Diels–Alder reactions, with complete facial selectivity being observed with all dienes investigated. The methodology surrounding these cycloadducts has been developed to allow for elaboration of these materials to functionalized, optically pure carbocyclic systems. Studies into the probable basis for the observed stereoselectivity as well as applications to the field of natural product synthesis are ongoing.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on an IBM/Bruker WP-270 spectrometer and are reported in δ-values, with *J*-values in Hz. M.p.s were obtained on a Mel-Temp melting point apparatus and are uncorrected. Microanalyses were performed by Desert Analytics of Tuscon, Az., and are within 0.4% of calculated values. IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrophotometer. All solvents were ACS reagent grade and were redistilled and dried according to standard procedures prior to use. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl.

Unsaturated Lactam **9**.—Dry THF (500 cm^3) was cooled to −78 °C in a 1 dm^3 flask under argon. To this was added 1.18 mol dm^{-3} $LiNPr_2^i$ (LDA) (157 cm^3, 185 mmol, 2.1 mol equiv.) dropwise. After 30 min a solution of lactam **8**‡ (16.1 g, 88.0 mmol) in dry THF (50 cm^3) was added dropwise. The reaction mixture was maintained at −78 °C for 2 h after which time methyl chloroformate (7.49 cm^3, 96.9 mmol, 1.1 mol equiv., distilled immediately before use) was added dropwise. The reaction mixture was stirred for 4 h at −78 °C, saturated aq. ammonium chloride (40 cm^3) was added, and the solution was allowed to warm to 25 °C. THF was removed under reduced pressure. The residue was partitioned between water and ethyl acetate, and the aq. phase was re-extracted with ethyl acetate (2 × 100 cm^3). The combined organic phases were dried (Na_2SO_4) and concentrated to yield diastereoisomeric methoxycarbonyl esters as a thick yellow oil (21.8 g). This material was used without further purification in the next step.

First, dry THF (150 cm^3) was cooled to −78 °C under argon, and 1.18 mol dm^{-3} LDA (20.4 cm^3, 24.1 mmol, 1.2 mol equiv.) was added dropwise. After 15 min a solution of diastereoisomeric methoxycarbonyl esters (4.84 g, 20.1 mmol) in dry THF (20 cm^3) was added dropwise. This mixture was maintained at −78 °C for 1.5 h, and a solution of benzeneselenenyl bromide was added dropwise. The latter solution was prepared from diphenyl diselenide (3.77 g, 12.0 mmol, 0.6 mol equiv.) and bromine (0.62 cm^3, 12.0 mmol, 0.6 mol equiv.) stirred for 2 h at 25 °C in THF (20 cm^3) prior to use. The solution was maintained at −78 °C for 4.5 h, saturated aq. ammonium chloride (10 cm^3) was added and the solution was warmed to 25 °C. The reaction mixture was filtered, and the solids were washed with diethyl ether. The resulting filtrate and washings were dried (Na_2SO_4), and the solvents were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (200 cm^3) and pyridine (4.88 cm^3, 59.9 mmol, 3.0 mol equiv.) was added. The solution was cooled to 0 °C, and 30% H_2O_2 (6.77 cm^3, 43.3 mmol, 21 mol equiv.) was added very cautiously, dropwise, to the vigorously stirred solution. The flask was placed in a refrigerator (8 °C) overnight. The stirred solution was then allowed to warm to 25 °C and the reaction mixture was then washed successively with cold 5% HCl, water, and saturated aq. NaCl (all 1 × 150 cm^3, in the order given). The resulting solution was dried (Na_2SO_4) and the solvents were removed under reduced pressure. The residue was chromatographed rapidly on silica gel with diethyl ether–hexene (3:1) as eluent to remove fast moving excess of benzeneselenenyl bromide. In this way, lactam **9** (3.38 g, 70% from **8**) was obtained as a light yellow oil, $[\alpha]_D$ +15.2° (*c* 2.01, acetone); $\nu_{max}(CCl_4)/cm^{-1}$ 2960, 2860, 1760 and 1730; *m/z* (NH_3 CI; 70 eV) (M + 1) 240 (Calc. 239); $\delta_H(CDCl_3)$ 7.67 (1 H, s), 4.32 (1 H, dd, *J* 8.8, 7.4), 4.08 (1 H, dd, *J* 8.9, 6.2), 3.86 (1 H, s), 3.57 (1 H, m), 1.75 (1 H, m), 1.58 (3 H, s), 1.09 (3 H, d, *J* 5.6) and 0.92 (3 H, d, *J* 5.6); $\delta_C(CDCl_3)$ 172.00, 161.47, 155.65, 130.91, 97.31, 73.67, 62,83, 52.00, 32.66, 21.98, 20.13 and 19.07; λ_{max}(MeCN)/nm 194 (ε 11 000) and 207 (8600) (Found: C, 60.05; H, 7.25; N, 5.85. Calc. for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85%).

Tricyclic Lactam **12n**.—The lactam **9** (425 mg, 1.78 mmol)

* Quenched dynamics MM2.

† 1 cal = 4.185 J.

‡ The compound is prepared from commercially available [*S*)-(+)-valinol and laevulinic acid by azeotropic removal of water; 86%, $[\alpha]_D$ +95.48° (*c* 2, EtOH). For further details see ref. 9.

was dissolved in 2,3-dimethylbuta-1,3-diene (2 g, 24.0 mmol, 14 mol equiv.) at 25 °C. The solution was heated at 65 °C for 8 h. The volatiles were removed under reduced pressure and the residue was chromatographed on silica gel with hexane–ethyl acetate (8:1) as eluent to give tricyclic lactam **12n** (508 mg, 89%) as an oil. On storage in the freezer, this material slowly crystallized to a solid, m.p. 87–88 °C; $[\alpha]_D$ −76.1° (*c* 3.45, acetone); $\nu_{max}(CCl_4)/cm^{-1}$ 2960, 2860, 1735 and 1705; *m/z* (NH_3 CI; 70 eV) (M + 1) 322 (calc. 321); $\delta_H(CDCl_3)$ 4.00 (1 H, dd, *J* 8.3, 8.3), 3.80 (1 H, dd, *J* 8.4, 6.1), 3.74 (3 H, s), 3.50 (1 H, m), 2.89 (1 H, dd, *J* 7.2, 3.4), 2.56 (1 H, d, *J* 14.4), 2.23 (2 H, m), 2.00 (1 H, m), 1.64 (1 H, m), 1.64 (6 H, s), 1.49 (3 H, s), 1.00 (3 H, d, *J* 6.7) and 0.85 (3 H, d, *J* 6.7); $\delta_C(CDCl_3)$ 175.89, 172.57, 127.74, 126.00, 98.83, 70.61, 61.83, 61.35, 52.53, 49.98, 34.51, 33.62, 29.11, 26.51, 20.23, 18.93, 18.81 and 18.38 (Found: C, 67.5; H, 8.7; N, 4.3. Calc. for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36%).

Unsaturated Lactam **17**.—To the lactam **8**[9] (1.56 g, 8.49 mmol) was added dry THF (50 cm^3) and the solution was cooled to −78 °C under argon. The solution was maintained at 78 °C for 1 h, and 1.38 mol dm^{-3} *sec*-BuLi (12.3 cm^3, 17.0 mmol, 2.0 mol equiv.) was then added dropwise. The solution was kept at −78 °C for 2.5 h and a solution of di-*tert*-butyl dicarbonate (2.05 cm^3, 8.91 mmol, 1.05 mol equiv.) in THF ~10 cm^3 was added dropwise. The reaction was quenched by the addition of saturated aq. ammonium chloride (5 cm^3). After 4 h the reaction mixture was then warmed to 25 C, the volatiles removed under reduced pressure, the residue was partitioned between diethyl ether and water, and the organic phase was dried (Na_2SO_4). Removal of the solvent an chromatography of the residue on silica gel with hexane–ethyl acetate (3:1) as eluent gave 1.29 g of diastereoisomeric *tert*-butoxycarbonyl esters. Part of this material (898 mg, 3.18 mmol) was dissolved in dry THF (35 cm^3) and the solution was cooled to −78 °C under argon. A solution of 1.38 mol dm^{-3} *sec*-BuLi (2.52 cm^3, 3.77 mmol, 1.19 mol equiv.) was added dropwise. After 30 min, and after an additional 1 h, solutions of PhSeBr (0.9 g, 3.77 mmol, 1.19 mol equiv.) in THF (5 cm^3) were added dropwise. After the mixture had been kept for 4 h at −78 °C saturated aq. NH_4Cl (5 cm^3) was added, and the solution was warmed to 25 °C. The volatiles were removed under reduced pressure and the residue was partitioned between diethyl ether and water. The organic phase was dried (Na_2SO_4) and the solvents were again removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (35 cm^3) and pyridine (0.77 cm^3, 9.56 mmol, 3.0 mol equiv.) was added. This solution was cooled to 0 °C and 30% H_2O_2 (1.07 cm^3, 6.86 mmol, 2.1 mol equiv.) was cautiously added dropwise to the vigorously stirred solution. The flask was placed in a refrigerator (8 °C) overnight. The stirred solution was then warmed to 25 °C, and washed successively with cold 5% HCl, water, and saturated aq. NaCl (all 1 × 75 cm^3, in the order given). The solution was dried (Na_2SO_4), and the solvents were removed under reduced pressure. The residue was chromatographed on silica gel [(5:1) hexane–ethyl acetate] to give compound **17** (668 mg, 42% from **8**) as an oil, $[\alpha]_D$ +13.5° (*c* 3.86, acetone); ν_{max}(neat)/cm^{-1} 2971, 2937, 2870, 1750 and 1728; $\delta_H(CDCl_3)$ 7.51 (1 H, s), 4.26 (1 H, dd, *J* 8.8, 7.6), 4.03 (1 H, dd, *J* 8.9, 6.0), 3.53 (1 H, ddd, *J* 10.1, 7.3, 6.0), 1.72 (1 H, m), 1.54 (3 H, s), 1.51 (9 H, s), 1.06 (3 H, d, *J* 6.6) and 0.89 (3 H, d, *J* 6.6); $\delta_C(CDCl_3)$ 172.15, 159.89, 154.28, 131.88, 96.87, 81.95, 73.44, 62.47, 32.52 (3 C), 27.71, 21.78, 20.08 and 18.94; λ_{max}(MeCN)/nm 192 (ε 11 000) and 210 (8800) (Found: C, 63.9; H, 8.4; N, 5.0. Calc. for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24; N, 4.98%).

Tricyclic Lactam **13**.—To the lactam **17** (249 mg, 0.89 mmol) was added 2,3-dimethylbuta-1,3-diene (1.54 g, 18.7 mmol, 21 mol equiv.). The resulting solution was maintained at gentle reflux for 5 h. The volatiles were removed under reduced pressure, and the residue was chromatographed on silica gel [(8:1) hexane–ethyl acetate] to give unchanged starting material **17** (33 mg) and tricyclic lactam **13** (235 mg, 94%) as a solid, m.p. 121–125 °C; $[\alpha]_D$ +58.0° (*c* 1.34, acetone); $\nu_{max}(CCl_4)/cm^{-1}$ 2972, 2929, 2874, 1733 and 1710; *m/z* (NH_3 CI; 70 eV) (M + 1) 364 (Calc. 363); $\delta_H(CDCl_3)$ 3.97 (1 H, dd, *J* 8.1, 8.1), 3.77 (1 H, dd, *J* 8.4, 5.9), 3.51 (1 H, ddd, *J* 10.7, 7.4, 6.0), 2.73 (1 H, dd, *J* 7.1, 3.6) 2.47 (1 H, d, *J* 14.6), 2.20 (2 H, m), 1.98 (1 H, m), 1.63 (6 H, s), 1.49 (3 H, s), 1.44 (9 H, s), 1.00 (3 H, d, *J* 6.7) and 0.84 (3 H, d, *J* 6.7); $\delta_H(C_6D_6)$ 171.40, 126.79, 99.04, 70.62, 62.57, 61.98, 49.56, 34.76, 34.18, 29.63, 27.90, 26.67, 20.49, 19.02, 18.85 and 18.59 (Found: C, 69.15; H, 9.34; N, 4.0. Calc. for $C_{21}H_{33}NO_4$: C, 69.39; H, 9.15; N, 3.85%).

Tricyclic Lactam **15**.—To the lactam **9** (36 mg, 0.15 mmol) was added benzene (0.8 cm^3), followed by 2-(*tert*-butyldimethylsiloxy)buta-1,3-diene (164 mg, 0.89 mmol, 6 mol equiv.). The solution was gently refluxed for 12 h. The volatiles were removed under reduced pressure, and the residue was chromatographed on silica gel [(6:1) hexane–ethyl acetate] to give unchanged **9** (15 mg) and tricyclic lactam **15** (34 mg, 89% based on recovered **9**) as an oil, $[\delta]_D$ +59° (*c* 1.1, acetone); $\nu_{max}(CCl_4)/cm^{-1}$ 2956, 2920, 2862, 2355, 1721 and 1670; $\delta_H(CDCl_3)$ 4.81 (1 H, dd, *J* 3.3, 1.7), 3.99 (1 H, dd, *J* 8.4, 7.2), 3.85 (1 H, dd, *J* 8.5, 5.2), 3.76 (3 H, s), 3.58 (1 H, ddd, *J* 10.4, 7.1, 5.1), 3.43 (1 H, s), 2.35–1.60 (4 H, m), 1.45 (3 H, s), 1.02 (3 H, d, *J* 6.6), 0.88 (12 H, s), 0.12 (3 H, s) and 0.09 (3 H, s); $\delta_C(CDCl_3)$ 173.67, 173.14, 151.51, 99.43, 77.21, 71.03, 61.31, 57.44, 52.79, 49.62, 32.92, 27.00, 25.99, 25.89, 25.62, 20.13, 19.12, 18.02, −4.37 and −4.66. This compound was unstable and did not give acceptable combustion analysis.

Tricyclic Lactam **16**.—To a mixture of the lactam **9** (51 mg, 0.21 mmol) and 2-(*tert*-butyldiphenylsiloxy)buta-1,3-diene (224 mg, 0.73 mmol, 3.5 mol equiv.) was added benzene (0.5 cm^3) and the mixture was heated at 65 °C for 5 h. The volatiles were then removed under reduced pressure and the residue was chromatographed on silica gel [(4:1) hexane–ethyl acetate] to furnish unchanged diene (162 mg) and tricyclic lactam **16** (125 mg, 100%) as a light yellow oil, $\delta_H(CDCl_3)$ 7.70 (4 H, m), 7.40 (6 H, m), 4.70 (1 H, dd, *J* 3.3, 1.4), 3.72 (3 H, s), 3.49 (1 H, dd, *J* 8.1, 4.4), 3.38 (1 H, ddd, *J* 10.6, 6.7, 4.6), 3.25 (2 H, m), 2.40–1.80 (4 H, m), 1.58 (1 H, m), 1.29 (3 H, s), 0.99 (9 H, s), 0.97 (3 H, d, *J* 6.6) and 0.83 (3 H, d, *J* 6.6). This compound was unstable and was not submitted for combustion analysis.

Tricyclic Lactam **18a**.—The lactam **17** (145 mg, 0.52 mmol) was dissolved in 2-(*tert*-butyldimethylsiloxy)buta-1,3-diene (1.39 mg, 7.53 mmol, 14 mol equiv.). The solution was then gently refluxed for 6 h. The volatiles were removed under reduced pressure and the residue was chromatographed on silica gel [(8:1) hexane–ethyl acetate] to give **18a** (214 mg, 89%) as a yellow oil, $\delta_H(CDCl_3)$ 4.79 (1 H, d, *J* 1.4), 3.95 (1 H, dd, *J* 8.2, 8.2), 3.82 (1 H, dd, *J* 4.9, 8.2), 3.55 (1 H, m), 3.31 (1 H, s) 2.30–1.50 (5 H, m), 1.45 (3 H, s), 1.43 (9 H, s), 1.03 (3 H, d, *J* 6.7), 0.87 (3 H, d, *J* 6.7), 0.86 (9 H, s), 0.09 (3 H, s) and 0.06 (3 H, s). This compound was unstable and was not submitted for combustion analysis.

Tricyclic Lactam **19**.—A solution of the lactam **9** (1.13 g, 4.73 mmol) in CH_2Cl_2 (35 cm^3) was cooled to −30 °C under argon. To this was added isoprene (4.73 cm^3, 47.3 mmol, 10 mol equiv.), followed by a solution of 1.0 mol dm^{-3} $ZnCl_2$ in diethyl ether (4.73 cm^3, 4.73 mmol, 1.0 mol equiv.) dropwise. The solution was allowed to warm to −10 °C, and maintained there for 4 h. The reaction mixture was warmed to 25 °C and diluted

with diethyl ether (200 cm^3) and then with water (75 cm^3). The phases were separated, and the lower, aq. phase was re-extracted with diethyl ether. The combined organic layers were dried (Na_2SO_4) and concentrated to yield a yellow oil (1.68 g). This material was chromatographed on silica gel [(6:1) hexane–ethyl acetate] to give compound **19** (1.0 g, 71%) as an oil which rapidly crystallized to a solid, m.p. 56–59 °C. The ratio of **19**:**20** as determined by capillary GC was 25.0:1, $[\alpha]_D$ +94.8° (*c* 2.01, acetone); ν_{max}(neat)/cm^{-1} 2951, 2880, 1741 and 1711; δ_H($CDCl_3$) 5.37 (1 H, m), 3.96 (1 H, dd, *J* 8.1, 8.1), 3.73 (1 H, dd, *J* 8.5, 6.2), 3.68 (3 H, s), 2.91 (1 H, dd, *J* 7.4, 3.4), 2.61 (1 H, dd, *J* 15.0, 6.3), 2.17 (1 H, dd, *J* 15.2, 3.6), 2.10 (1 H, m), 1.88 (1 H, dd, *J* 15.2, 7.4), 1.62 (3 H, s), 1.60 (1 H, m), 1.43 (3 H, s), 0.93 (3 H, d, *J* 6.6) and 0.78 (3 H, d, *J* 6.6); δ_C($CDCl_3$) 176.23, 172.47, 137.14, 119.13, 98.71, 70.48, 61.82, 60.31, 52.58, 48.21, 33.55, 28.12, 27.04, 26.13, 22.48, 20.23 and 18.85 (Found: C, 66.2; H, 8.3; N, 4.4. Calc. for $C_{17}H_{25}NO_4$: C, 66.43; H, 8.20; N, 4.56%).

Tricyclic Lactam **21**.—To the lactam **9** (1.63 g, 6.82 mmol) were added CH_2Cl_2 (40 cm^3) and technical myrcene (9.1 g, 68.2 mmol, 10 mol equiv.). The solution was cooled to 0 °C, and 1.0 mol dm^{-3} $ZnCl_2$ in diethyl ether (6.82 cm^3, 6.82 mmol, 1.0 mol equiv.) was added dropwise. After 36 h at 0 °C the solution was warmed to 25 °C and diluted with diethyl ether (200 cm^3) and water (50 cm^3). The phases were separated and the lower, aq. phase was re-extracted with diethyl ether. The combined diethyl ether phases were dried (Na_2SO_4) and the solvents were removed under reduced pressure to yield a yellow oil (13 g). This material was chromatographed rapidly on silica gel (to remove excess of myrcene before it could polymerize on the column) on elution with (8:1) hexane–ethyl acetate. Thus compound **21** was obtained as an oil (1.7 g, 66%). The ratio of **21**:**22** as determined by capillary GC was 15.2:1, $[\alpha]_D$ +51° (*c* 4.8, acetone); ν_{max}(neat)/cm^{-1} 2964, 2931, 2875, 1741 and 1713; δ_H($CDCl_3$) 5.45 (1 H, m), 5.05 (1 H, m), 4.01 (1 H, dd, *J* 8.1, 8.1), 3.77 (1 H, dd, *J* 8.5, 6.3), 3.74 (3 H, s), 3.50 (1 H, m), 2.94 (1 H, dd, *J* 7.3, 4.0), 2.67 (1 H, dd, *J* 15.0, 6.2), 2.21 (2 H, m), 2.00 (5 H, m), 1.64 (3 H, s), 1.56 (3 H, s), 1.48 (3 H, s), 0.99 (3 H, d, *J* 6.6) and 0.84 (3 H, d, *J* 6.6); δ($CDCl_3$) 176.05, 172.54, 140.96, 131.24, 124.08, 118.69, 98.69, 70.55, 61.65, 60.57, 52.59, 48.35, 36.66, 33.65, 28.06, 26.11, 26.01, 25.46, 20.27, 18.83, 17.50 and 15.10 (Found: C, 70.4; H, 8.8; N, 3.5. Calc. for $C_{22}H_{33}NO_4$: C, 70.37; H, 8.86; N, 3.73%).

Tricyclic Lactam **23**.—The lactam **9** (51 mg, 0.21 mmol) was dissolved in toluene (2 cm^3) and diphenylbuta-1,3-diene (230 mg, 1.1 mmol, 5.0 mol equiv.) was added. The resulting solution was refluxed for 12 h, and the solvent was removed under reduced pressure. The residue was triturated with (6:1) hexane–ethyl acetate, releasing some of the excess of diene as a solid. The filtrate was chromatographed on silica gel [(6:1) hexane–ethyl acetate] to give compound **23** (80 mg, 86%) as a crystalline solid, m.p. 132–133 °C; $[\alpha]_D$ −74.6° (*c* 1.25, acetone); ν_{max}(CCl_4)/cm^{-1} 3030, 2970, 2880, 1750, 1725 and 1560; *m*/*z* (NH_3 CI: 70 eV) (M + 1) 446 (Calc. 445); δ_H($CDCl_3$) 7.30 (10 H, m), 5.89 (1 H, ddd, *J* 13.1, 10.1, 3.6), 5.80 (1 H, ddd, *J* 13.1, 10.1, 3.6), 4.32 (1 H, dd, *J* 8.3, 8.3), 4.22 (1 H, dd, *J* 5.7, 2.7), 3.93 (1 H, dd, *J* 8.6, 6.4), 3.75 (1 H, m), 3.35 (1 H, d, *J* 8.6), 3.23 (3 H, s), 1.66 (1 H, m), 1.32 (3 H, s), 1.01 (3 H, d, *J* 6.6) and 0.90 (3 H, d, *J* 6.4); δ_C($CDCl_3$) 170.93, 145.82, 140.65, 131.76, 130.33, 130.07, 128.85, 128.54, 128.27, 128.01, 127.74, 127.11, 126.42, 99.15, 71.45, 60.24, 52.90, 52.01, 42.54, 37.57, 33.76, 26.05, 20.22 and 19.01 (Found: C, 75.2; H, 6.95; N, 3.15. Calc. for $C_{28}H_{31}NO_4$: C, 75.48; H, 7.01; N, 3.14%).

Tricyclic Lactam **25**.—To the lactam **9** (1.21 g, 5.08 mmol) was added (*E*,*E*)-hexa-2,4-diene (5.0 g, 60.9 mmol, 12 mol equiv.), and the solution was heated for 8 h at 70 °C. The volatiles were then removed under reduced pressure and the residue was chromatographed slowly on silica gel [(6:1) hexane–ethyl acetate] to give pure lactam **25** (353 mg) followed by a mixture of compounds **25** and **26** (894 mg), and then pure compound **26** (173 mg, 87%). Lactam **25** was a crystalline solid, m.p. 79–82 °C recrystallized (hexane) m.p. 90–91 °C; $[\alpha]_D$ +73.3° (*c* 1.42, acetone); ν_{max}(CCl_4) 2965, 2943, 2878, 1736 and 1709; δ_H($CDCl_3$) 5.73 (1 H, ddd, *J* 8.7, 3.5, 3.5), 5.45 (1 H, ddd, *J* 8.8, 3.5, 3.5), 3.96 (1 H, dd, *J* 8.1, 8.1), 3.77 (3 H, s), 3.67 (1 H, dd, *J* 8.4, 6.2), 3.49 (1 H, ddd, *J* 10.8, 7.8, 6.3), 2.68 (1 H, d, *J* 5.9), 2.66 (1 H, m), 2.38 (1 H, m), 1.60 (1 H, m), 1.43 (3 H, d, *J* 6.8), 1.40 (3 H, s), 1.36 (3 H, d, *J* 7.3), 1.00 (3 H, d, *J* 6.6) and 0.82 (3 H, d, *J* 6.6); δ_C($CDCl_3$) 175.75, 172.86, 136.02, 130.95, 98.44, 69.68, 64.84, 61.31, 57.36, 52.42, 35.60, 33.74, 31.85, 28.67, 20.38, 18.99, 16.51 and 15.00 (Found: C, 67.5; H, 8.45; N, 4.2. Calc. for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36%).

Tricyclic Lactam **26**.—For preparation of this material see the experimental procedure for tricyclic lactam **25**. Data for tricyclic lactam **26**: an oil, $[\alpha]_D$ 23.7° (*c* 1.30, acetone); ν_{max}(CCl_4)/cm^{-1} 2968, 2876, 1740 and 1715; δ_H($CDCl_3$) 5.58 (2 H, m), 4.15 (1 H, dd, *J* 7.9, 7.9), 3.83 (1 H, dd, *J* 8.9, 6.9), 3.71 (3 H, s), 3.63 (1 H, m), 2.45 (1 H, m), 2.32 (1 H, s), 2.27 (1 H, m), 1.67 (1 H, m), 1.43 (3 H, s), 1.22 (3 H, d, *J* 6.9), 1.20 (3 H, d, *J* 6.2), 1.04 (3 H, d, *J* 6.6) and 0.86 (3 H, d, *J* 6.6); δ_C($CDCl_3$) 176.04, 172.15, 133.10, 132.02, 98.28, 70.52, 63.49, 60.92, 56.79, 52.00, 33.84, 32.55, 27.93, 27.06, 21.42, 20.36, 18.91 and 17.00 (Found: C, 67.3; H, 8.5; N, 4.4. Calc. for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36%).

Tetracyclic Lactam **31**.—To the lactam **9** (104 mg, 0.42 mmol) were added CH_2Cl_2 (2.5 cm^3) and then cyclohexa-1,3-diene (269 mg, 3.40 mmol, 8 mol equiv.). The resulting solution was cooled to −20 °C, and 1.0 mol dm^{-3} $SnCl_4$ in toluene (84 mm^3, 0.084 mmol, 0.2 mol equiv.) was added dropwise. After the mixture had been kept 17 h at −20 °C, diethyl ether (10 cm^3) and water (2 cm^3) were added. The phases were separated and the lower, aq. phase was re-extracted with diethyl ether. The combined diethyl ether phases were dried (Na_2SO_4), and the solvents were removed under reduced pressure. The resulting residue was chromatographed on silica gel [(4:1) hexane–ethyl acetate] to yield tetracyclic lactams **29** and **30** as an inseparable 1.0:1 mixture (100 mg, 75%). After several runs a portion of this mixture (120 mg, 0.376 mmol) was dissolved in absolute ethanol (6 cm^3) and 10% Pd/C (35 mg) was added. The resulting suspension was hydrogenated at 3 atm for 3 h. The reaction mixture was then purged with argon, and additional 10% Pd/C (35 mg) was added. After a further 3 h hydrogenation, the reaction was observed to be complete, by capillary GC to give a single product. The reaction mixture was filtered through Celite and the solvents were removed under reduced pressure to yield compound **31** (111 mg, 92%) as an oil, $[\alpha]_D$ +97.7° (*c* 6.77, acetone); ν_{max}(neat)/cm^{-1} 2944, 2867, 1739 and 1717; δ_H($CDCl_3$) 4.27 (1 H, dd, *J* 8.3, 8.3), 3.87 (1 H, dd, *J* 8.4, 7.6), 3.74 (3 H, s), 3.60 (1 H, m), 2.80 (1 H, s), 2.37 (1 H, s), 1.96 (1 H, s), 1.72–1.11 (8 H, m), 1.51 (3 H, s), 0.99 (3 H, d, *J* 6.6) and 0.84 (3 H, d, *J* 6.6); δ_C($CDCl_3$) 173.85, 171.87, 99.85, 71.13, 62.08, 60.57, 52.80, 49.14, 34.36, 29.61, 26.45, 25.88, 24.82, 22.19, 21.90, 20.52, 20.32 and 18.75 (Found: C, 67.4; H, 8.25; N, 4.5. Calc. for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.46; N, 4.36%).

Epoxide **34**.—The lactam **12n** (482 mg, 1.43 mmol) was dissolved in CH_2Cl_2 (11 cm^3) at 25 °C. To this was added Na_2HPO_4 (407 mg, 2.87 mmol, 2.0 mol equiv.), followed by 85% *m*-chloroperbenzoic acid (320 mg, 1.58 mmol, 1.1 mol equiv.). The reaction mixture was stirred under argon at 25 °C for 3 h and was then filtered through Celite, and the filtrate was

washed successively with 1 mol dm^{-3} NaOH, 20% aq. $Na_2S_2O_3$, and saturated aq. NaCl (all 1 × 10 cm^3, in the order given). The resulting solution was dried (Na_2SO_4), and the solvents were removed under reduced pressure to yield a yellow oil (222 mg). A column of Matrex© silica gel was conditioned as follows prior to use. The column was washed with hexane–ethyl acetate–triethylamine (300 cm^3, 20 column volumes) (4:1:1). The column was then washed with (3:1) hexane-ethyl acetate (300 cm^3) until the eluent pH had dropped to 6. The mixed epoxides were then applied to the column and were eluted with (3:1) hexane–ethyl acetate. Thus the major epoxide **34** (140 mg) was obtained, followed by mixed fractions containing epoxides **34** and **35** (31 mg), and then minor epoxide **35** (10 mg, 82%). Major epoxide **34** crystallized in the freezer to a solid, m.p. 77–78 °C; $[\alpha]_D$ +102° (*c* 2.21, acetone); ν_{max}(neat)/cm^{-1} 2956, 1750, 1711, 1272, 1217, 1019, 883 and 772; $\delta_H(C_6D_6)$ 3.83 (1 H, dd, *J* 7.9, 7.9), 3.60 (1 H, m), 3.40 (1 H, dd, *J* 7.9, 7.0), 3.36 (3 H, s), 3.25 (1 H, dd, *J* 11.4, 8.2), 3.08 (1 H, d, *J* 14.6), 2.03 (1 H, dd, *J* 14.7, 11.3), 1.86 (1 H, d, *J* 14.8), 1.82 (1 H, dd, *J* 14.7, 8.2), 1.38 (1 H, m), 1.32 (3 H, s), 1.09 (3 H, s), 1.06 (3 H, d, *J* 6.5), 1.02 (3 H, s) and 0.52 (3 H, d, *J* 6.5); δ_C (C_6D_6), 178.03, 171.55, 99.27, 69.91, 63.27, 58.97, 58.62, 56.85, 52.53, 43.80, 34.77, 34.16, 27.65, 24.29, 20.75, 18.83, 18.44 and 18.21 (Found: C, 64.1; H, 8.1; N, 3.9. Calc. for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15%).

Epoxide **35**.—For preparation of this material see the experimental procedure for epoxide **35**. Data for epoxide **35**: oil, $[\alpha]_D$ +75.6° (*c* 1.09, acetone); ν_{max}(neat)/cm^{-1} 2956, 2933, 2878, 1744, 1717, 1261, 1233, 904, 855 and 840; $\delta_H(C_6D_6)$ 4.24 (1 H, dd, *J* 7.8, 7.8), 3.89 (1 H, m), 3.62 (1 H, dd, *J* 7.9, 6.1), 3.25 (3 H, s), 3.04 (1 H, d, *J* 14.6), 2.69 (1 H, dd, *J* 8.1), 2.27 (1 H, dd, *J* 14.9), 1.97 (1 H, d, *J* 14.6), 1.48 (2 H, m), 1.48 (3 H, s), 1.12 (3 H, d, *J* 6.6), 1.04 (6 H, s) and 0.54 (3 H, d, *J* 6.6); $\delta_C(C_6D_6)$ 176.30, 172.48, 98.46, 70.78, 64.07, 58.78, 58.26, 56.76, 52.17, 45.75, 34.58, 34.13, 28.54, 27.99, 20.68, 19.05, 18.32 and 18.21 (Found: C, 63.8; H, 8.05; N, 3.9. Calc. for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15%).

The Alcohol **36a**.—To the lactam **12n** (6.34 mg, 1.96 mmol) was added absolute ethanol (20 cm^3), the mixture was cooled to −5 °C under argon, and $NaBH_4$ (300 mg, 7.85 mmol, 4 mol equiv.) was added neat, all at once. The mixture was maintained at 25 °C for 7 h, and the suspension was then allowed to warm to 25 °C. After 7 h at 25 °C, the mixture was treated with water (3 cm^3), and the volatiles were removed under reduced pressure. The residue was dissolved in ethyl acetate (40 cm^3) and the solution was cooled to 0 °C and treated dropwise with 0.5 mol dm^{-3} HCl (20 cm^3). After 20 min the phases were separated, and the aq. phase was re-extracted with ethyl acetate. The combined organic layers were washed successively with saturated aq. $NaHCO_3$ and saturated aq. NaCl (both 1 × 30 cm^3). The solution was then dried (Na_2SO_4), and the solvents were removed under reduced pressure. The resulting residue was chromatographed on silica gel [(3:1) hexane–ethyl acetate]. In this way compound **36a** (518 mg, 90%) was obtained as an oil, $[\alpha]_D$ +150° (*c* 1.84, Et_2O); $\nu_{max}(CCl_4)$/cm^{-1} 3460, 2995, 2960, 2880 and 1705; $\delta_H(CDCl_3)$ 3.94 (1 H, dd, *J* 8.2, 8.2), 3.74 (1 H, dd, *J* 8.3, 6.1), 3.69 (1 H, d, *J* 10.8), 3.52 (1 H, d, *J* 10.8), 3.48 (1 H, m), 2.36 (1 H, dd, *J* 7.1, 3.7), 2.23 (1 H, dd, *J* 7.1, 4.0), 2.18 (1 H, d, *J* 13.8), 1.93 (1 H, dd, *J* 14.0, 7.4), 1.80 (1 H, d, *J* 14.5), 1.64 (3 H, s), 1.61 (3 H, s), 1.46 (3 H, s), 0.99 (3 H, d, *J* 6.6) and 0.84 (3 H, d, *J* 6.6); $\delta_C(CDCl_3)$ 182.77, 128.01, 125.63, 99.10, 69.97, 67.98, 65.69, 62.73, 56.12, 46.82, 34.50, 33.61, 29.32, 26.58, 20.50, 19.02, 18.43 and 15.16; $\delta_C(C_6D_6)$ 182.92, 126.03, 99.35, 70.02, 67.71, 62.77, 57.07, 47.02, 34.92, 34.02, 29.74, 26.51, 20.91, 19.27, 19.06 and 18.64 (Found: C, 69.6; H, 9.3; N, 4.6. Calc. for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.27; N, 4.7%).

The Alcohol **36b**.—Tricyclic lactam **19** (950 mg, 3.09 mmol) was dissolved in absolute ethanol (13 cm^3) and the solution was cooled to −5 °C under argon and $NaBH_4$ (351 mg, 9.27 mmol, 3.0 mol equiv.) was added neat, all at once. After 5 min the suspension was allowed to warm to 25 °C. The reaction mixture was kept 6 h at 25 °C, diluted with absolute ethanol (40 cm^3), and placed in a 600 cm^3 beaker. To this stirred solution was cautiously added glacial acetic acid (2.33 cm^3, 40.8 mmol, 1.6 mol equiv., H^+/equiv. H^-). The clear solution was stirred for 15 min at 25 °C, and the volatiles were removed under reduced pressure. The residue was partitioned between 5% HCl and ethyl acetate and the phases were separated. The aq. phase was then re-extracted with ethyl acetate (2 × 75 cm^3). The combined ethyl acetate layers were washed successively with saturated aq. $NaHCO_3$ and with saturated aq. NaCl (both 1 × 100 cm^3). The solution was dried (Na_2SO_4) and concentrated to yield a yellow oil (900 mg). Chromatography of this material on silica gel [(3:1) hexane–ethyl acetate] yielded compound **36b** (762 mg, 88%) as an oil, $[\alpha]_D$ +85.2° (*c* 2.02, acetone); ν_{max}(neat)/cm^{-1} 3428, 2966, 2946, 2875 and 1689; $\delta_H(CDCl_3)$ 5.38 (1 H, m), 3.96 (1 H, dd, *J* 8.1, 8.1), 3.70 (2 H, m), 3.50 (2 H, m), 2.48 (1 H, dd, *J* 7.6, 3.4), 2.37 (1 H, s), 2.21 (3 H, m), 1.93 (1 H, dd, *J* 15.5, 7.5), 1.73 (1 H, m), 1.67 (3 H, s), 1.45 (3 H, s), 0.98 (3 H, d, *J* 6.6) and 0.82 (3 H, d, *J* 6.6); $\delta_C(CDCl_3)$ 183.45, 137.49, 119.03, 99.08, 69.84, 67.82, 62.91, 54.95, 45.74, 33.66, 28.06, 27.10, 26.00, 22.64, 20.62 and 18.99 (Found: C, 68.6; H, 9.2; N, 4.9. Calc. for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01%).

The Alcohol **36c**.—The lactam **21** (1.70 g, 4.53 mmol) was suspended in absolute ethanol (19 cm^3) at 25 °C and then cooled to −5 °C under argon. Once the mixture had equilibrated, $NaBH_4$ (515 mg, 13.6 mmol, 3.0 mol equiv.) was added neat, all at once. The flask was maintained for 15 min at −5 °C, the bath was removed and the suspension was allowed to warm to 25 °C. After 19 h, the mixture was diluted with absolute ethanol (60 cm^3) and placed in a 600 cm^3 beaker. To this stirred solution was added glacial acetic acid dropwise (3.74 cm^3, 65.5 mmol, 1.3 mol equiv., H^+/equiv. H^-). After being stirred for 15 min at 25 °C the volatiles were removed under reduced pressure. The residue was partitioned between 5% HCl and ethyl acetate, and the aq. phase was re-extracted with ethyl acetate (2 × 75 cm^3). The combined organic phases were washed successively with saturated aq. $NaHCO_3$ and saturated aq. NaCl (both 1 × 200 cm^3). The resulting solution was dried (Na_2SO_4) and concentrated to yield a yellow oil (1.6 g). The oil was chromatographed on silica gel [(2:1) hexane–ethyl acetate] to yield compound **36c** (1.21 g, 77%) as an oil, $[\alpha]_D$ +86.6° (*c* 7.34, acetone); ν_{max}(neat)/cm^{-1} 3435, 2955, 2934, 2873, 1706 and 1683; $\delta_H(CDCl_3)$ 5.42 (1 H, m), 5.05 (1 H, m, 3.99 (1 H, dd, *J* 8.1, 8.1), 3.73 (1 H, dd, *J* 8.1, 5.3), 3.69–3.49 (3 H, m), 2.39 (1 H, dd, *J* 7.4, 4.5), 2.30–1.81 (8 H, m), 1.65 (1 H, m), 1.65 (3 H, s), 1.57 (3 H, s), 1.47 (3 H, s), 1.00 (3 H, d, *J* 6.6) and 0.84 (3 H, d, *J* 6.6); $\delta_C(CDCl_3)$ 183.25, 141.37, 131.22, 124.29, 118.61, 99.01, 69.87, 67.91, 62.64, 55.33, 45.95, 36.81, 33.73, 27.83, 26.14, 26.00, 25.60, 20.67, 18.97 and 17.62 (Found: C, 73.0; H, 9.4; N, 4.2. Calc. for $C_{21}H_{33}NO_3$: C, 72.59; H, 9.57; N, 4.03%).

Tosyl Ester **37a**.—To the alcohol **38a** (2.2 g, 7.51 mmol) was added CH_2Cl_2 (75 cm^3) at 25 °C, and the solution was treated with triethylamine (2.2 cm^3, 15.8 mmol, 2 mol equiv.), 4-(dimethylamino)pyridine (DMAP) (50 mg), and tosyl chloride (1.58 g, 8.29 mmol, 1.6 mol equiv.) in the order given. After 24 h at 25 °C the mixture was treated with water (10 cm^3) and stirred vigorously for 10 min. The volatiles were then removed under reduced pressure and the residue was dissolved in ethyl acetate. This solution was then extracted successively with saturated aq. $NaHCO_3$, 10% HCl, and saturated aq. NaCl (all 1 × 20 cm^3, in the order given). The solution was dried (Na_2SO_4) and the

solvents were removed under reduced pressure. The residue was chromatographed on silica gel [(5:1) hexane–ethyl acetate] to yield the tosate **37a** (3.32 g, 99%) as an oil which crystallized on storage in the freezer to give a solid, m.p. 67–70 °C; $[\alpha]_D$ +40.4° (*c* 1.40, acetone); $\nu_{max}(CCl_4)/cm^{-1}$ 2980, 2850, 1710 and 1600; $\delta_H(C_6D_6)$ 7.82 (2 H, d, *J* 8.2), 6.79 (2 H, d, *J* 8.2), 4.10 (2 H, dd, *J* 31.6, 9.1), 3.67 (1 H, dd, *J* 6.0, 6.0) 3.50 (2 H, m), 2.53 (1 H, dd, *J* 6.8, 2.3), 2.30 (1 H, dd, *J* 14.7, 1.9), 2.20 (1 H, d, *J* 13.9), 1.89 (3 H, s), 1.73 (3 H, s), 1.70 (3 H, m), 1.66 (3 H, s), 1.48 (3 H, s), 1.11 (3 H, d, *J* 6.6) and 0.57 (3 H, d, *J* 6.6); $\delta_H(CDCl_3)$ 7.71 (2 H, d, *J* 6.8), 7.29 (2 H, d, *J* 6.8), 3.95 (3 H, m), 3.72 (1 H, dd, *J* 8.5, 6.2), 3.43 (1 H, ddd, *J* 10.7, 7.7, 6.2), 2.50 (1 H, dd, *J* 7.1, 3.4), 2.41 (3 H, s), 2.21 (1 H, dd, *J* 14.8, 3.3), 2.03 (1 H, d, *J* 13.5), 1.92 (2 H, m), 1.70 (1 H, m), 1.61 (3 H, s), 1.54 (3 H, s), 1.44 (3 H, s), 0.94 (3 H, d, *J* 6.7) and 0.81 (3 H, d, *J* 6.7); $\delta_C(C_6D_6)$ 179.38, 144.50, 134.24, 129.91, 128.90, 125.09, 98.88, 73.51, 69.97, 62.83, 54.59, 46.80, 34.49, 33.86, 29.58, 26.41, 21.13, 20.59, 19.05, 18.91 and 18.48 (Found: C, 64.2; H, 7.6; N, 3.1. Calc. for $C_{24}H_{33}NO_5S$: C, 64.40; H, 7.43; N, 3.13%).

Tricyclic Lactam **38**.—To the cyclopropane **39** (3.92 mg, 14.3 mmol) was added CH_2Cl_2 (75 cm^3), the solution cooled to −78 °C under argon, and TMSI (2.42 cm^3, 17.1 mmol, 1.2 mol equiv.) was added dropwise. The reaction flask was placed in a −27 °C freezer overnight. This cold solution was then poured into a separatory funnel containing diethyl ether (250 cm^3) and the resulting solution was extracted with 20% aq. $Na_2S_2O_3$ and saturated aq. NaCl (both 1 × 150 cm^3, in the order given). This solution was then dried (Na_2SO_4) and concentrated to yield crude iodide **51** (5.77 g), which was used immediately in the subsequent step.

Compound **51** (5.77 g, taken as 14.3 mmol) was dissolved in methanol (105 cm^3) at 25 °C, and treated with magnesium (1.78 g, 71.5 mmol, 5 mol equiv.). The suspension was stirred vigorously under argon (slight exotherm) for 3 h, and was then added to water (100 cm^3). This mixture was treated cautiously with 1 mol dm^{-3} HCl (100 cm^3). After being vigorously stirred for 15 min the solution was extracted with diethyl ether (3 × 150 cm^3). The combined diethyl ether phases were dried (K_2CO_3), and the solvents were removed under reduced pressure. This residue was then immediately chromatographed on silica gel and eluted with (10:1) hexane–ethyl acetate. In this way more lactam **38** (2.45 g, 62% over 2 steps) was obtained as a pale yellow oil, $[\alpha]_D$ +79.5° (*c* 2.34, acetone); $\nu_{max}(CCl_4)/cm^{-1}$ 2950, 2920, 2860 and 1710; $\delta_H(CDCl_3)$ 3.92 (1 H, dd, *J* 8.1, 8.1), 3.72 (1 H, dd, *J* 8.5, 6.1), 3.47 (1 H, ddd, *J* 10.6, 7.6, 6.1), 2.20 (3 H, m), 1.93 (2 H, m), 1.62 (1 H, m), 1.60 (6 H, s), 1.43 (3 H, s), 1.25 (3 H, s), 0.97 (3 H, d, *J* 6.7) and 0.82 (3 H, d, *J* 6.7); $\delta_C(CDCl_3)$ 184.19, 127.27, 98.46, 70.03, 61.94, 51.89, 49.83, 39.36, 33.61, 29.48, 27.79, 26.21, 20.34, 19.06 and 18.34 (Found: C, 73.9; H, 10.0; N, 5.1. Calc. for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05%).

Cyclopropane **39**.—A solution of tosate **37a** (112 mg, 0.25 mmol) in DMSO (2.5 cm^3) was placed in an 80 °C thermostatted bath and stirred for 9 h. The reaction mixture was then cooled to 25 °C and diluted with water (5 cm^3). The resulting solution was extracted with diethyl ether (4 × 20 cm^3), and the combined organic layers were washed with saturated aq. ammonium chloride (1 × 25 cm^3). The solution was dried (Na_2SO_4), and concentrated to yield compound **39** (71 mg, 100%) as a light yellow oil which slowly crystallized in the freezer to a solid, m.p. 62–63 °C; $[\alpha]_D$ +91° (*c* 2.3, acetone); $\delta_{max}(CCl_4)/cm^{-1}$ 2960, 2930, 2870, 1720, 1465 and 1378; FAB HRMS M(H^+) (Found: *m/z*, 276.1959. Calc. for $C_{17}H_{26}NO_2$: *m/z* 276.1964); $\delta_H(CDCl_3)$ 4.12 (1 H, dd, *J* 8.4, 8.4), 3.71 (1 H, dd, *J* 8.4, 7.2), 3.55 (1 H, m), 2.65 (1 H, d, *J* 17), 2.50 (1 H, d, *J* 17), 2.25 (2 H, dd, *J* 15, 15), 1.59 (6 H, s), 1.55 (1 H, m), 1.42 (3 H, s), 1.15 (1 H, d, *J* 4.2), 1.02 (1 H, d, *J* 4.2), 0.95 (3 H, d, *J* 6.5) and 0.82 (3 H, d, *J* 6.5); $\delta_C(CDCl_3)$ 121.08, 120.44, 99.67, 69.81, 62.67, 33.76, 29.22, 27.74, 23.98, 20.55, 19.38 and 19.05 (Found: C, 73.9; H, 9.1; N, 5.0. Calc. for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09%).

Tosylate **37b**.—A solution of the lactam **36b** (816 mg, 2.92 mmol) in CH_2Cl_2 (30 cm^3) at 25 °C was treated with DMAP (85 mg) triethylamine (0.86 cm^3, 6.2 mmol, ~2 mol equiv.), and tosyl chloride (618 mg, 3.24 mmol, ~1.1 mol equiv.) in the order given. The solution was stirred for 11 h at 25 °C and further DMAP (30 mg) was added. The mixture was maintained at 25 °C for an additional 24 h, and water (30 cm^3) was added. The solution was stirred vigorously and was then concentrated. The residue was treated with ethyl acetate (50 cm^3) and the phases were separated with ethyl acetate (3 × 50 cm^3). The organic phases were washed successively with saturated aq. sodium hydrogen carbonate, water, and saturated aq. sodium chloride (all 1 × 150 cm^3, in the order given). The resulting solution was dried (Na_2SO_4), concentrated, and chromatographed on silica gel [(2:1) hexane–ethyl acetate] to yield the tosate **37b** (1.13 g, 89%) as an oil, $[\alpha]_D$ +57.2° (*c* 2.21, acetone); ν_{max}(neat)/cm^{-1} 2967, 2878, 1706, 1600, 1461, 1444, 1367, 1300 and 1239; $\delta_H(CDCl_3)$ 7.71 (2 H, d, *J* 8.3), 7.29 (2 H, d, *J* 8.3), 5.30 (1 H, dd, *J* 3.5, 1.8), 3.95 (1 H, m), 3.94 (2 H, s), 3.71 (1 H, dd, *J* 8.4, 6.2), 3.44 (1 H, m), 2.58 (1 H, dd, *J* 7.4, 3.2), 2.41 (3 H, s), 2.24 (1 H, dd, *J* 15.1, 3.2), 2.14 (1 H, dd, *J* 13.5, 5.5), 1.92 (1 H, dd, *J* 14.9, 7.3), 1.66 (3 H, s), 1.63 (2 H, m), 1.45 (3 H, s), 0.96 (3 H, d, *J* 6.6) and 0.81 (3 H, d, *J* 6.6); $\delta_C(CDCl_3)$ 179.98, 144.96, 138.43, 132.80, 129.90, 127.87, 118.10, 98.72, 73.28, 69.92, 62.66, 53.38, 45.49, 33.75, 27.83, 27.19, 25.85, 22.57, 21.58, 20.48 and 19.01 (Found: C, 63.7; H, 7.3; N, 3.3. Calc. for $C_{23}H_{31}NO_5S$: C, 63.72; H, 7.21; N, 3.23%).

Tosylate **37c**.—To a solution of the alcohol **36c** (1.2 g, 3.46 mmol) in CH_2Cl_2 (35 cm^3) at 25 °C were added DMAP (100 mg), triethylamine (1.02 cm^3, 7.32 mmol, ~2 mol equiv.), and tosyl chloride (0.732 g, 3.84 mmol, 1.1 mol equiv.) in the order given. The resulting solution was stirred under argon at 25 °C for 17 h, and additional DMAP (30 mg) was added. The solution was maintained at 25 °C for a further 8 h, added to water (25 cm^3), and stirred vigorously. The reaction mixture was then concentrated, ethyl acetate (50 cm^3) was added to the residue, and the phases were separated. The aq. layer was re-extracted with ethyl acetate (2 × 75 cm^3) and the combined organic phases were washed separately with saturated aq. sodium hydrogen carbonate, water, and saturated aq. sodium chloride (all 1 × 150 cm^3, in the order given). This solution was dried (Na_2SO_4) and concentrated to yield tosylate **37c** (1.62 g, 93%) as a light yellow oil, $[\alpha]_D$ +52.6° (*c* 3.20, acetone); ν_{max}/cm^{-1} 2962, 2930, 2874, 2360, 2342, 1709, 1598, 1456, 1358 and 1362; $\delta_H(CDCl_3)$ 7.71 (2 H, d, *J* 8.4), 7.30 (2 H, d, *J* 8.0), 5.33 (1 H, m), 5.01 (1 H, m), 3.93 (2 H, dd, *J* 15.1, 9.1), 3.92 (1 H, m), 3.70 (1 H, dd, *J* 8.5, 6.3), 3.45 (1 H, ddd, *J* 10.7, 7.6, 6.5), 2.54 (1 H, dd, *J* 7.3, 4.1), 2.41 (3 H, s), 2.30–1.50 (8 H, m), 1.64 (3 H, s), 1.55 (3 H, s), 1.46 (3 H, s), 0.96 (3 H, d, *J* 6.6) and 0.81 (3 H, d, *J* 6.6); $\delta_C(CDCl_3)$ 179.79, 144.91, 142.21, 132.90, 131.43, 129.89, 127.86, 124.14, 117.64, 98.66, 73.44, 69.94, 62.49, 53.64, 45.65, 36.69, 33.78, 27.80, 26.29, 26.07, 25.84, 25.56, 21.55, 20.46, 18.98 and 17.60. (Found: C, 66.9; H, 8.0; N, 2.7. Calc. for $C_{28}H_{39}NO_5S$: C, 67.04; H, 7.84; N, 2.79%).

Cyclopropane **40**.—Tosylate **37b** (982 mg, 2.27 mmol) was dissolved in DMSO (20 cm^3) at 25 °C and the solution was placed in an 82 °C thermostatted bath. The mixture was stirred for 11 h at this temperature, cooled to 25 °C, and added to water (100 cm^3). The solution was then extracted well with diethyl ether (6 × 75 cm^3). The combined extracts were washed with

saturated aq. sodium chloride (1 × 300 cm^3), dried (Na_2SO_4) and concentrated to yield a yellow oil (657 mg). Rapid chromatography of this material on silica gel [(2:1) hexane–ethyl acetate] gave compound **40** as a light yellow oil (599 mg, 100%), $[\alpha]_D$ +112° (*c* 1.87, acetone); ν_{max}(neat)/cm^{-1} 2960, 2933, 2913, 2874, 1720, 1467 and 1448; δ_H($CDCl_3$) 5.20 (1 H, m), 4.12 (1 H, dd, *J* 8.3, 8.3), 3.70 (1 H, dd, *J* 8.6, 7.2), 3.55 (1 H, m), 2.68–2.12 (4 H, m), 1.63 (3 H, s), 1.55 (1 H, m), 1.42 (3 H, s), 1.17 (1 H, d, *J* 4.2), 1.07 (1 H, d, *J* 4.2), 0.94 (3 H, d, *J* 6.5) and 0.81 (3 H, d, *J* 6.5); δ_C($CDCl_3$) 185.12, 128.76, 116.54, 99.53, 69.75, 62.59, 36.21, 33.73, 27.51, 25.78, 23.78, 23.66, 23.05, 20.52, 19.20 and 19.01 (Found: C, 73.1; H, 8.8; N, 5.2. Calc. for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36%).

Cyclopropane **41**.—A solution of tosate **37c** (1.11 g, 2.22 mmol) in DMSO (8 cm^3) was placed in a 90 °C thermostatted bath. The solution was stirred under argon at this temperature for 4 h, cooled to 25 °C, and water (20 cm^3) was added. The solution thus obtained was extracted well with diethyl ether (5 × 40 cm^3), and the combined extracts were washed with saturated aq. sodium chloride (1 × 150 cm^3). The solution was dried (Na_2SO_4) and concentrated to yield a yellow oil. Immediate chromatography of this oil on silica gel [(8:1) hexane–ethyl acetate] gave compound **41** (667 mg, 91%) as a nearly colourless oil, $[\alpha]_D$ +85.4° (*c* 5.16, acetone); ν_{max}(neat)/cm^{-1} 2966, 2862, 1717, 1468, 1449, 1378, 1336 and 1312; δ_H($CDCl_3$) 5.22 (1 H, m), 5.02 (1 H, m), 4.13 (1 H, dd, *J* 8.3, 8.3), 3.71 (1 H, dd, *J* 8.5, 8.5), 3.53 (1 H, m), 2.75–1.85 (8 H, m), 1.65 (3 H, s), 1.60 (1 H, m), 1.56 (3 H, s), 1.42 (3 H, s), 1.14 (1 H, d, *J* 4.1), 1.09 (1 H, d, *J* 4.2), 0.94 (3 H, d, *J* 6.5) and 0.82 (3 H, d, *J* 6.5); δ_C($CDCl_3$) 184.99, 132.73, 131.49, 123.91, 116.44, 99.50, 69.65, 62.53, 37.88, 36.21, 33.68, 27.78, 26.49, 25.53, 24.21, 23.18, 23.02, 20.46, 19.17, 18.98 and 17.57 (Found: C, 76.6; H, 9.4; N, 4.2. Calc. for $C_{21}H_{31}NO_2$: C, 76.55; H, 9.48; N, 4.25%).

Tosylate **45**.—A solution of the alcohol **44** (0.54 g, 1.66 mmol) in CH_2Cl_2 (15 cm^3) at 25 °C was treated with DMAP (20 mg), triethylamine (0.49 cm^3, 3.5 mmol, ~2 mol equiv.), and tosyl chloride (0.35 g, 1.83 mmol, ~1.6 mol equiv.) in the order given. The solution was maintained at 25 °C for 12 h, further DMAP (20 mg) was added, and the solution was stirred for an additional 24 h. Water (6 cm^3) was then added, and the mixture was stirred vigorously for 15 min and then concentrated. The residue was dissolved in ethyl acetate and extracted successively with saturated aq. sodium hydrogen carbonate and saturated aq. sodium chloride (both 1 × 150 cm^3). The solution was then dried (Na_2SO_4), and filtered through Florisil which was then washed with ethyl acetate. Evaporation of solvent provided tosate **45** (754 mg, 95%) as a viscous yellow oil, of approximately 93% purity (capillary GC). Owing to the instability of this compound on silica gel, only ^1H NMR data were obtained: δ_H($CDCl_3$) 7.75 (2 H, d, *J* 8.3), 7.32 (2 H, d, *J* 8.4), 4.10 (1 H, dd, *J* 8.3, 8.0), 4.05 (2 H, d, *J* 2.9), 3.87 (4 H, s), 3.77 (1 H, dd, *J* 8.6, 6.5), 3.56 (1 H, m), 2.56 (1 H, dd, *J* 12.2, 6.3), 2.42 (3 H, s), 1.88–1.16 (7 H, m), 1.47 (3 H, s), 0.95 (3 H, d, *J* 6.6) and 0.84 (3 H, d, *J* 6.6).

Cyclopropane **46**.—A solution of tosate **46** (355 mg, 0.740 mmol) in DMSO (5 cm^3) was heated at 82 °C for 24 h. The solution was diluted with water (6 cm^3) and extracted well with diethyl ether (6 × 15 cm^3). The combined extracts were washed with saturated aq. sodium chloride (1 × 50 cm^3), dried (Na_2SO_4), and concentrated to yield compound **46** (221 mg, 97%) as a yellow oil. Owing to the instability of this compound on silica gel, only ^1H NMR data were obtained: δ_H($CDCl_3$) 4.16 (1 H, dd, *J* 8.5, 8.5), 3.72 (1 H, dd, *J* 8.7, 7.2), 3.60 (1 H, m), 3.00 (1 H, d, *J* 17.6), 2.67 (1 H, dt, *J* 14.1, 6.4), 2.50 (1 H, d, *J* 17.5), 2.34–1.90 (3 H, m), 1.57 (1 H, m), 1.46 (1 H, dd, *J* 5.4, 0.7), 1.39 (3 H, s), 1.21 (1 H, d, *J* 5.6), 0.94 (3 H, s), 1.21 (1 H, d, *J* 5.6), 0.94 (3 H, d, *J* 6.5) and 0.84 (3 H, d, *J* 6.6).

Diketone **48**.—To a solution of lactam **39** (71 mg, 0.25 mmol) in dry THF (10 cm^3) at −78 °C was added 1.67 mol dm^{-3} n-BuLi (0.45 cm^3, 0.75 mmol, 3 mol equiv.). The solution was stored in a −27 °C freezer for 12 h and was then quenched with saturated aq. ammonium chloride (1 cm^3). The reaction mixture was warmed to 25 °C, then concentrated, and the residue was partitioned between water and diethyl ether. The aq. phase was extracted well with diethyl ether and the combined organic phases were washed with saturated aq. sodium chloride (1 × 50 cm^3), dried (Na_2SO_4), and concentrated to yield enamine **47** (90 mg, 100%). To this material were added absolute ethanol (4 cm^3) and 1 mol dm^{-3} $Bu_4NH_2PO_4$ (4 cm^3) and the solution was stirred for 1 h at 25 °C and for 5 h at reflux. The reaction mixture was concentrated, diluted with water (5 cm^3), and extracted well with diethyl ether (4 × 10 cm^3). The combined organic layers were washed with saturated aq. sodium chloride (1 × 50 cm^3), dried (Na_2SO_4) and concentrated to yield a yellow oil (70 mg). Chromatography of this material [(4:1) hexane–ethyl acetate] on silica gel provided compound **48** (61 mg, 98% over two steps) as a light yellow oil, $[\alpha]_D$ −5.6° (*c* 6.1, acetone); ν_{max}(CCl_4)/cm^{-1} 2960, 2935, 2870, 1702, 1695 and 1445; δ_H(C_6D_6) 2.53 (2 H, d, *J* 15.5), 2.35 (2 H, m), 1.95 (2 H, m), 1.95 (3 H, s), 1.78 (1 H, d, *J* 3.7), 1.60 (2 H, m), 1.40 (6 H, s), 1.25 (2 H, m), 0.88 (1 H, d, *J* 3.7) and 0.84 (3 H, t, *J* 7.3); δ_C(C_6D_6) 208.03, 205.86, 122.13, 122.03, 41.26, 40.95, 40.47, 33.86, 33.70, 28.21, 26.09, 22.66, 19.80, 19.03 and 14.04. This material was not further characterized but was used immediately in the synthesis of carbocycle **49**.

Carbocycle **49**.—A solution of diketone **48** (50 mg, 0.20 mmol) in absolute ethanol (1 cm^3) was treated with a solution of NaOEt [sodium (3 mg, 0.10 mmol, 0.5 mol equiv.) in absolute ethanol (1 cm^3)]. The mixture was stirred for 24 h at 25 °C and then concentrated. The residue was partitioned between water and diethyl ether, and the aq. phase was re-extracted with diethyl ether (3 × 10 cm^3). The combined organic phases were washed with saturated aq. sodium chloride (1 × 25 cm^3), dried (Na_2SO_4), and concentrated to yield carbocycle **49** (42 mg, 91%) as a yellow oil, $[\alpha]_D$ +48° (*c* 4.0, acetone); ν_{max}(CCl_4)/cm^{-1} 2962, 2935, 2878, 2840, 1700, 1632 and 1445; FAB HRMS M(H^+) Found: *m/z*, 231.1751. Calc. for $C_{16}H_{23}O$: *m/z* 231.1749; δ_H(C_6D_6) 2.60 (1 H, d, *J* 18.5), 2.45 (1 H, d, *J* 18.5), 2.10 (4 H, m), 1.60 (3 H, s), 1.45 (2 H, m), 1.44 (6 H, s), 1.02 [1 H, d, *J* 2.8), 0.92 (1 H, d, *J* 2.8) and 0.82 (3 H, t, *J* 7.3); δ_C(C_6D_6) 206.08, 167.58, 134.02, 122.71, 120.60, 40.55, 32.54, 31.33, 29.99, 29.85, 25.09, 22.13, 19.38, 19.22, 13.99 and 13.20; ν_{max}(MeCN)/nm 215 (ε 8100) and 270 (3000).

Tricyclic Lactam **54**.—A solution of lactam **40** (328 mg, 1.25 mmol) in CH_2Cl_2 (6.5 cm^3) was cooled to −78 °C under argon and treated dropwise with TMSI (214 cm^3, 1.50 mmol, 1.2 mol equiv.). The mixture was kept for 18 h at −27 °C, and then poured into a separatory funnel containing diethyl ether (50 cm^3). The solution was immediately washed successively with 20% $Na_2S_2O_3$ (1 × 50 cm^3) and saturated sodium chloride (1 × 50 cm^3). The organic phase was dried (Na_2SO_4) and concentrated to yield iodide **52** (480 mg) as a yellow oil.

This material (1.25 mmol) was immediately dissolved in absolute methanol (9 cm^3) and treated with magnesium powder (156 mg, 6.30 mmol, 5 mol equiv.). The mixture was stirred at 25 °C for 3.5 h, diluted with methanol (20 cm^3), and added to stirred water (15 cm^3). The resulting slurry was treated with 1 mol dm^{-3} HCl (15 cm^3), stirred vigorously for 15 min, and concentrated. Ethyl acetate (100 cm^3) was added to this residue, and the aq. phase was extracted well with ethyl acetate (3 × 50

cm^3). The combined extracts were washed successively with saturated aq. sodium hydrogen carbonate (1 × 150 cm^3) and saturated aq. sodium chloride (1 × 150 cm^3), dried (Na_2SO_4), and concentrated to yield a yellow oil (338 mg). This oil was chromatographed on silica gel [(10:1) hexane–ethyl acetate] to yield lactam **54** (195 mg, 59% over two steps) as a yellow oil, $[\alpha]_D$ +101° (*c* 1.04, acetone); ν_{max}(neat)/cm^{-1} 2961, 2872, 2833, 1712, 1460, 1444 and 1378; $\delta_H(C_6D_6)$ 5.54 (1 H, m), 3.65 (1 H, dd, *J* 7.5, 7.5), 3.56 (1 H, m), 3.39 (1 H, dd, *J* 7.7, 7.5), 2.61 (1 H, dd, *J* 14.5, 6.1), 2.25 (1 H, dd, *J* 14.8, 2.5), 1.92 (1 H, dd, *J* 7.5, 2.6), 1.79 (1 H, dd, *J* 15.9, 7.5), 1.73 (3 H, s), 1.18 (3 H, s), 1.08 (3 H, d, *J* 6.6) and 0.52 (3 H, d, *J* 6.5); $\delta_C(CDCl_3)$ 184.83, 136.85, 120.62, 98.44, 69.91, 62.15, 51.12, 48.76, 33.65, 32.78, 27.36, 26.44, 22.61, 20.45 and 19.02 (Found: C, 72.9; H, 9.6; N, 5.1. Calc. for $C_{16}H_{25}NO_2$: C, 72.97; H, 9.57; N, 5.32%).

Tricyclic Lactam **55**.—A solution of the cyclopropane **41** (471 mg, 1.43 mmol) in CH_2Cl_2 (7.5 cm^3) was cooled to −78 °C under argon and was treated dropwise with TMSI (245 cm^3, 1.72 mmol, 1.2 mol equiv.). The solution was stored for 18 h at −27 °C and was then added to a separatory funnel containing diethyl ether (50 cm^3). The solution was washed immediately with 20% $Na_2S_2O_3$ (1 × 100 cm^3) and saturated aq. sodium chloride (1 × 100 cm^3). The resulting solution was dried (Na_2SO_4), filtered through Celite, and concentrated to yield crude iodide **53** (650 mg, 100%).

This material (650 mg, 1.43 mmol) was immediately dissolved in absolute methanol (10 cm^3) and treated with magnesium powder (178 mg, 7.21 mmol, 5 mol equiv.). The suspension was stirred for 4 h at 25 °C, diluted with methanol (20 cm^3), and added to stirred water (15 cm^3). The slurry obtained was treated with 1 mol dm^{-3} HCl (15 cm^3), stirred vigorously for 30 min, and concentrated. Ethyl acetate (75 cm^3) was added to the residue, and the aq. phase was extracted well with ethyl acetate (3 × 50 cm^3). The combined ethyl acetate layers were washed successively with saturated aq. sodium hydrogen carbonate (1 × 150 cm^3) and saturated aq. sodium chloride (1 × 150 cm^3), dried (Na_2SO_4), and concentrated to yield a dark yellow oil (469 mg). This oil was immediately chromatographed on silica gel [(8:1) hexane–ethyl acetate] to give lactam **55** (289 mg, 61% over two steps) as a light yellow oil, $[\alpha]_D$ +85.6° (*c* 4.41, acetone); ν_{max}(neat)/cm^{-1} 2967, 2922, 2867, 1711 and 1451; $\delta_H(CDCl_3)$ 5.46 (1 H, m), 5.03 (1 H, m), 3.95 (1 H, dd, *J* 8.4, 8.4), 3.71 (1 H, dd, *J* 8.5, 6.3), 3.49 (1 H, m), 2.35–1.85 (9 H, m), 1.70 (1 H, m), 1.63 (3 H, s), 1.55 (3 H, s), 1.44 (3 H, s), 1.27 (3 H, s), 0.99 (3 H, d, *J* 6.6), and 0.83 (3 H, d, *J* 6.6); $\delta_C(CDCl_3)$ 184.64, 140.74, 131.24, 124.40, 121.19, 98.43, 70.00, 61.97, 51.37, 49.09, 36.81, 33.77, 32.69, 27.42, 26.70, 26.46, 26.23, 25.62, 20.49, 19.02 and 17.64 (Found: C, 76.3; H, 10.3; N, 4.25. Calc. for $C_{21}H_{33}NO_2$: C, 76.09; H, 10.03; N, 4.23%).

Carbocycle **58**.—A solution of lactam **54** (184 mg, 0.699 mmol) in dry THF (6.5 cm^3) was cooled to −78 °C and was then treated dropwise with 1.47 mol dm^{-3} BuLi (1.43 cm^3, 2.10 mmol, 3 mol equiv.). The reaction mixture was stored for 20 h at −27 °C, quenched with saturated aq. ammonium chloride (4 cm^3), warmed to 25 °C, and concentrated. The residue was treated with water (15 cm^3) and diethyl ether (30 cm^3), and the aq. phase was extracted well with diethyl ether (3 × 30 cm^3). The combined extracts were washed with saturated aq. sodium chloride (1 × 150 cm^3), dried (Na_2SO_4), and concentrated to give crude enamine (230 mg) as a yellow oil. This oil was immediately dissolved in absolute ethanol (3 cm^3), 1 mol dm^{-3} $Bu_4NH_2PO_4$ (13 cm^3, 13 mmol) was added, and the suspension was stirred for 1 h at 25 °C and for 8 h at reflux. The reaction mixture was then cooled to 25 °C, concentrated, and diethyl ether (30 cm^3) was added to the residue. The aq. phase was extracted well with diethyl ether (3 × 30 cm^3), and the combined ether phases were washed with saturated aq. sodium chloride (1 × 100 cm^3), dried (Na_2SO_4), and concentrated to yield crude diketone **57** (177 mg) as a yellow oil. This oil was immediately dissolved in absolute ethanol (6.5 cm^3) and treated dropwise with a solution of NaOEt [sodium (8 mg, 0.35 mmol, ~0.5 mol equiv.) in absolute ethanol (17 cm^3)]. The solution was stirred for 14 h at 25 °C, concentrated, and the residue was partitioned between water and diethyl ether. The aq. phase was re-extracted with diethyl ether (3 × 25 cm^3) and the combined ether phases were dried (Na_2SO_4) and concentrated to yield a yellow oil (164 mg). Immediate chromatography of this oil on silica gel [(10:1) pentane–diethyl ether] provided carbocycle **58** 84.4 mg, (55% over three steps) as a light yellow oil, $[\alpha]_D$ +19.8° (*c* 1.91, acetone); ν_{max}(neat)/cm^{-1}: 2961, 2933, 2872, 1694, 1644 and 1447; $\delta_H(CDCl_3)$ 5.39 (1 H, m), 2.49 (1 H, m), 2.32–1.97 (6 H, m), 1.93 (3 H, s), 1.70 (1 H, m), 1.59 (3 H, s), 1.32 (2 H, m), 1.02 (3 H, s) and 0.77 (3 H, t, *J* 7.3); $\delta_C(CDCl_3)$ 213.04, 169.27, 140.60, 134.70, 121.44, 51.89, 47.23, 33.55, 30.72, 24.98, 23.95, 23.11, 21.46, 14.83 and 13.50; ν_{max}(MeCN)/nm 95 (ε 9300) and 233 (10 000) (Found: C, 82.78; H, 10.3. Calc. for $C_{15}H_{22}O$: C, 82.52; H, 10.16%).

Carbocycle **61**.—A solution of lactam **55** (273 mg, 0.824 mmol) in dry THF (7.5 cm^3) at −78 °C was treated dropwise with 1.47 mol dm^{-3} BuLi (1.68 cm^3, 2.47 mmol, 3 mol equiv.). The mixture was kept 18 h at −27 °C, quenched with saturated aq. ammonium chloride (4 cm^3), and warmed to 25 °C. The solution was concentrated, the residue was treated with water (15 cm^3) and diethyl ether (30 cm^3), and the aq. phase was extracted well with diethyl ether (3 × 30 cm^3). The combined ether phases were washed with saturated aq. sodium chloride (1 × 150 cm^3), dried (Na_2SO_4), and concentrated to yield crude enamine **59** (337 mg) as a yellow oil. This oil was immediately dissolved in absolute ethanol (3.5 cm^3), 1 mol dm^{-3} $Bu_4NH_2PO_4$ (15 cm^3, 15 mmol) was added, and the suspension was stirred for 1 h at 25 °C and for 8 h at reflux before being cooled to 25 °C and concentrated; diethyl ether was added to the residue (30 cm^3). The aq. phase was extracted well with diethyl ether (3 × 30 cm^3), and the combined ether phases were washed with saturated aq. sodium chloride (1 × 100 cm^3), dried (Na_2SO_4), and concentrated to yield crude diketone **60** (337 mg) as a yellow oil. This oil was immediately dissolved in absolute ethanol (7.5 cm^3) and treated dropwise with a solution of NaOEt [sodium (10 mg, 0.44 mmol, 0.5 mol equiv.) in absolute ethanol (20 cm^3)]. The mixture was stirred 14 h at 25 °C, then concentrated, and the residue was partitioned between water (25 cm^3) and diethyl ether (25 cm^3). The aq. phase was extracted well with diethyl ether (3 × 25 cm^3), and the combined ether phases were dried (Na_2SO_4) and concentrated to yield a yellow oil (287 mg). This material was immediately chromatographed on silica gel [(5:1) pentane–diethyl ether] to yield carbocycle **61** (144 mg, 61% over three steps) as a light yellow oil, $[\alpha]_D$ +43.6° (*c* 2.76, acetone); ν_{max}(neat)/cm^{-1} 2960, 2930, 2871, 1699, 1647 and 1451; $\delta_H(CDCl_3)$ 5.42 (1 H, m), 5.00 (1 H, m), 2.50 (1 H, m), 2.35–1.52 (10 H, m), 1.95 (3 H, s), 1.63 (3 H, s), 1.54 (3 H, s), 1.34 (2 H, m), 1.03 (3 H, s) and 0.79 (1 H, t, *J* 7.3); $\delta_C(CDCl_3)$ 212.91, 169.02, 140.69, 138.78, 131.53, 124.02, 121.18, 52.10, 47.47, 37.14, 33.36, 29.73, 26.33, 25.59, 25.08, 24.14, 21.51, 17.60, 14.86 and 13.68; ν_{max}(MeCN)/nm 234 (ε 13000) (Found: C, 83.8; H, 10.7. Calc. for $C_{20}H_{30}O$: C, 83.86; H, 10.56%).

Tricyclic Lactam **42**.—To a solution of lactam **18b** (3.88 mg, 12.6 mmol) in dry THF (60 cm^3) at −5 °C was added 1 mol dm^{-3} Bu_4NF (15.1 cm^3, 15.1 mmol, 1.2 mol equiv.) dropwise. The reaction was stirred for 5 min at −5 °C, water (10 cm^3) was added, and the solution was warmed to 25 °C before being concentrated. The residue was partitioned between water and

CH_2Cl_2, and the aq. layer was extracted with CH_2Cl_2 (2 × 75 cm^3). The combined CH_2Cl_2 layers were washed with saturated aq. sodium chloride (1 × 150 cm^3), dried (Na_2SO_4), and concentrated to yield a yellow oil (3.41 g). This oil was passed through a column of Florisil [(1:1) hexane–ethyl acetate] to yield lactam **42** (3.21 g, 82%) as a solid, m.p. 70–72 °C after one recrystallization from (1:1) diethyl ether–pentane; $[\alpha]_D$ +170° (*c* 0.37, acetone); $\nu_{max}(CCl_4)/cm^{-1}$ 2959, 2877, 2280, 1737 and 1716; $\delta_H(CDCl_3)$ 4.12 (1 H, dd, *J* 8.6, 8.6), 3.81 (3 H, s), 3.76 (1 H, dd, *J* 7.1, 7.1), 3.65 (1 H, m), 3.22 (1 H, dd, *J* 6.8, 4.5), 2.67–2.40 (2 H, m), 2.40–1.85 (4 H, m), 1.70 (1 H, m), 1.52 (3 H, s), 1.07 (3 H, d, *J* 6.4) and 0.88 (H, d, *J* 6.4); $\delta_C(C_6D_6)$ 206.24, 176.87, 171.58, 98.61, 70.02, 63.18, 57.30, 52.49, 45.43, 35.93, 35.61, 34.07, 26.03, 24.69, 20.66 and 18.72 (Found: C, 61.9; H, 7.7; N, 4.4. Calc. for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53%).

Tricyclic Lactam **43**.—A solution of lactam **42** (61 mg, 0.20 mmol) and toluene-*p*-sulphonic acid (6 mg) in dry benzene (6 cm^3) was treated with ethylene glycol (56 cm^3, 1.0 mmol, 5 mol equiv.) and heated to reflux in a Dean–Stark apparatus for 1.5 h. The solution was then cooled to 0 °C and added to ice–saturated aq. sodium hydrogen carbonate (10 cm^3), and the aq. phase was extracted well with diethyl ether (3 × 10 cm^3). The combined extracts were washed with saturated aq. sodium chloride (1 × 30 cm^3), dried (Na_2SO_4), and concentrated to yield crude compound **43** (63 mg, 89%) as a highly unstable yellow oil. Attempted distillation or chromatography of this compound caused complete decomposition, hence only ^1H NMR data were obtained: $\delta_H(CDCl_3)$ 4.17 (1 H, dd, *J* 8.4, 8.4), 3.92 (1 H, m), 3.91 (4 H, s), 3.74 (3 H, s), 3.63 (1 H, ddd, *J* 13.6, 9.8, 6.9), 3.05 (1 H, dd, *J* 12.7, 6.1), 2.38–1.50 (5 H, m), 1.38 (3 H, s), 1.01 (3 H, d, *J* 6.6) and 0.87 (3 H, d, *J* 6.6).

Alcohol **44**.—To a solution of lactam **43** (96 mg, 0.27 mmol) in diethyl ether (5 cm^3) was added 2.0 mol dm^{-3} $LiBH_4$ (0.14 cm^3, 0.28 mmol, 1 mol equiv.), followed by 1.0 mol dm^{-3} $LiBEt_3H$ (30 cm^3, 0.03 mmol, 0.6 mol equiv.). The solution was stirred for 2 h at 25 °C, quenched with half-saturated aq. ammonium chloride (3 cm^3), and stirred vigorously for 10 min. The phases were then separated, and the aq. portion was extracted with diethyl ether (2 × 20 cm^3). The combined diethyl ether phases were washed with saturated aq. sodium chloride (1 × 50 cm^3), dried (Na_2SO_4) and concentrated to yield crude alcohol **44** (69 mg, 78%) as an oil. This material was highly unstable and only ^1H NMR data were obtained: $\delta_H(CDCl_3)$ 4.13 (1 H, dd, *J* 8.6, 7.9), 3.90 (4 H, m), 3.82 (1 H, dd, *J* 8.7, 6.4), 3.73 (2 H, d, *J* 7.7), 3.59 (1 H, ddd, *J* 10.5, 7.6, 6.7), 2.39 (1 H, dd, *J* 12.3, 6.2), 1.88–1.58 (7 H, m), 1.51 (3 H, s), 1.00 (3 H, d, *J* 6.7) and 0.86 (3 H, d, *J* 6.6).

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