Synthesis of [*n*]polynorbornanes with differing edge substitution: a new class of regioselectively addressable framework †

Frederick M. Pfeffer *[a] **and Richard A. Russell** [b]

[a] *Department of Chemistry, Trinity College, Dublin, D2, Ireland. E-mail: pfefferf@tcd.ie.; Fax: +353 1 671 2826; Tel: +353 1 608 1306*
[b] *Centre for Chiral and Molecular Technologies, Deakin University, Geelong, 3216, Australia. E-mail: rarcat@deakin.edu.au.; Fax: +61 3 925 17492; Tel: +61 3 925 17454*

Received (in Cambridge, UK) 24th June 2002, Accepted 17th October 2002
First published as an Advance Article on the web 5th November 2002

Polynorbornanes with differing edge functionality have been synthesised from the appropriate cyclobutene epoxides substituted with two, unlike, electron withdrawing groups. These latter compounds were prepared by the monohydrolysis of symmetric cyclobutene diesters and subsequent elaboration of the resulting carboxylic acid.

Introduction

In a previous paper we have described [*n*]polynorbornane frameworks as rigid templates to which peptides can be attached in a regiospecific manner *i.e.* RAFTS[1] (see Fig. 1).[2]

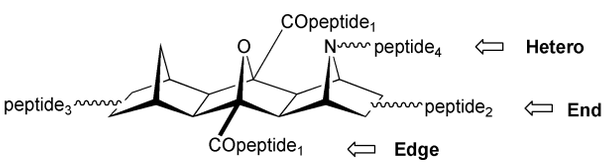


Fig. 1 Sites for attachment to [*n*]polynorbornanes.

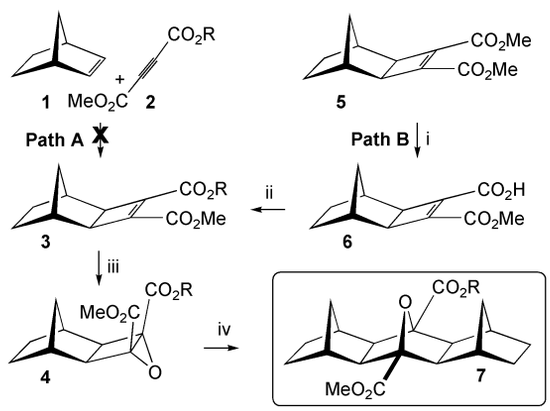
The construction of these frameworks was based upon the ACE (Alkene + Cyclobutene Epoxide) reaction which involves the thermal ring opening of cyclobutene epoxides and subsequent 1,3-dipolar cycloaddition of the resulting carbonyl ylide to a functionalised norbornene.[3]

We have identified strategies to attach peptides to such templates at a variety of points (see Fig. 1). Whilst the introduction of unlike functionality at the end positions is readily accomplished, we have to date been unable to synthesise any frameworks that have unlike edge substitutions and it is this topic which is addressed in the present communication.

Results and discussion

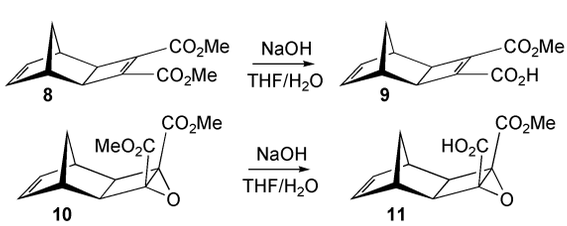
Our first approach to a simple model system, the mixed ester **7**, focussed upon the Mitsudo coupling[4] of the appropriate esters of acetylenedicarboxylic acid with norbornenes (Scheme 1, Path A). This strategy suffered from two defects. Firstly the starting esters **2** were tedious to synthesise[5] and second, as a result of this, only small amounts of the pivotal cyclobutene **3** could be prepared.

As a consequence of these findings we turned our attention to the hydroxide mediated monohydrolysis of the readily available dimethyl ester **5** (Scheme 1, Path B). When this reaction was conducted in aqueous tetrahydrofuran according to the method of Niwayama[6] the desired monocarboxylic acid



Scheme 1 Approaches to [3]polynorbornanes with differentiated edges. *Reagents and conditions for R = Bn*: (i) 0.25 M NaOH, THF–H_2O, 1 h. (ii) BnOH, DiPCDI, DMAP, DCM, 12 h. (iii) ^{t}BuOOH, ^{t}BuOK, THF, 12 h. (iv) Sealed tube, DCM, 6 h.

6 could be isolated in 78% yield. Subsequent re-esterification of this acid with benzyl alcohol using diisopropylcarbodiimide (DiPCDI) as the coupling agent proceeded smoothly as did the remaining steps of the ACE sequence leading to the [3]polynorbornane **7** (R=Bn). Similarly the norbornadiene derivative **8** afforded the corresponding monoacid **9** in 92% isolated yield (Scheme 2).

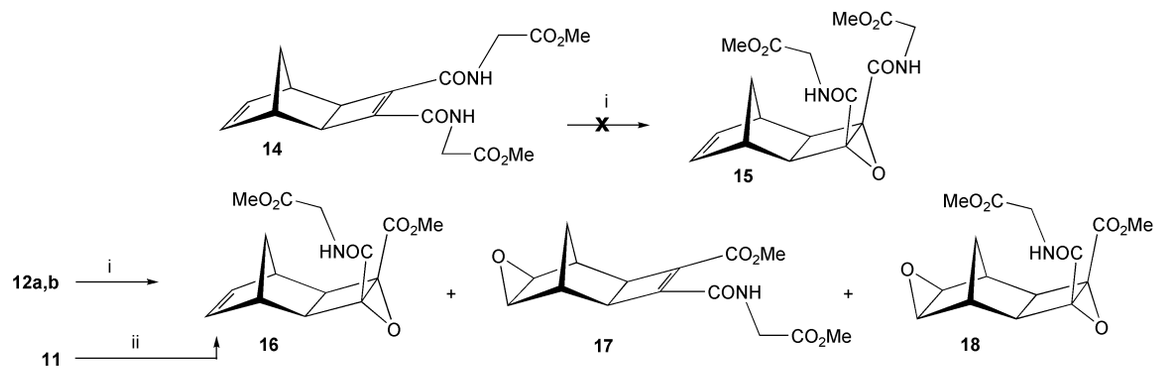


Scheme 2 Desymmetrisation by means of partial hydrolysis of diesters.

In contrast the diester epoxide **10** (Scheme 2) was a far less satisfactory starting material and gave variable yields of the monocarboxylic acid **11**, which never exceeded 54%. This significantly lower yield was not associated with the presence of the epoxide functionality, which we have previously shown to be stable to base,[2] but rather appeared to be a function of

† The term RAFT has been coined to describe such frameworks; RAFT is an acronym for Regioselectively Addressable Functionalised Template.[1]

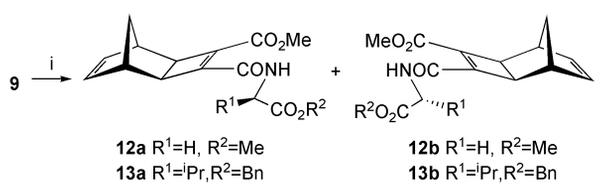
 DOI: 10.1039/b206057d



Scheme 4 Epoxidation reaction. *Reagents and conditions*: (i) ^{t}BuOOH, ^{t}BuOK, THF, 12 h. (ii) DiPCDI, DMAP, DMF, GlyOMe, 12 h.

the relatively poor solubility of the starting material in the predominantly aqueous solvent. Indeed it is our experience that this is a general limitation of the otherwise excellent Niwayama methodology.

Having established an entrée to edge differentiation we next turned our attention to the timely addition of peptide chains. The monocarboxylic acid **9** (Scheme 3) underwent carbodiimide



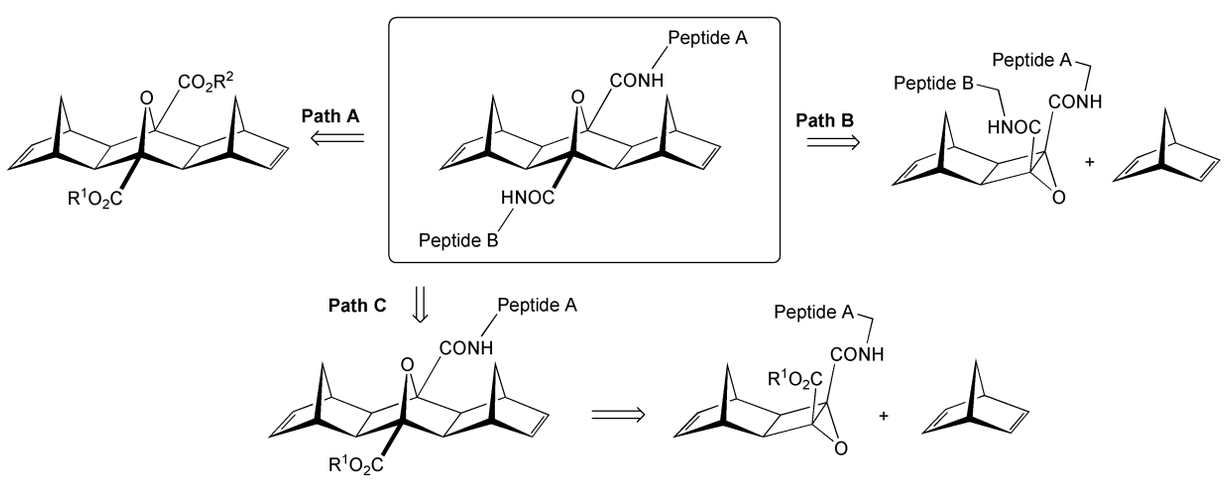
Scheme 3 Coupling of amino acids. *Reagents and conditions*: (i) DiPCDI, amino acid ester, DMF, 12 h.

mediated condensation with a variety of amino acid esters to afford coupled products such as **12a**,**b** in moderate (60–70%) yield. In cases involving chiral amino acids *e.g.* (*S*)-valine the resultant product contained two diastereomers **13a**,**b** that could be separated by careful chromatography to afford a new source of chiral BLOCKS‡ for further elaboration in ACE reactions.

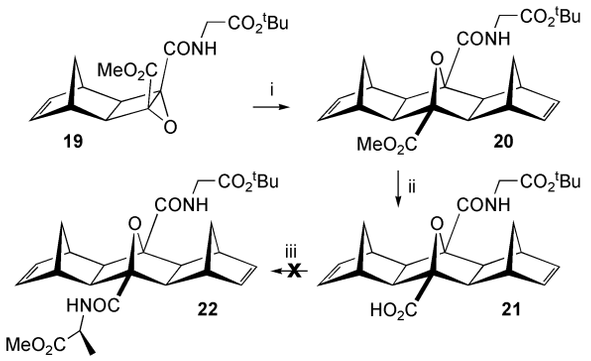
Significantly, and unlike our previous experience with cyclobutene bis-amides which resist epoxidation entirely (*e.g.* **14**, Scheme 4),[7] the amide-esters **12** upon treatment with ^{t}BuOOH and ^{t}BuOK in THF afforded the corresponding epoxide **16** in good yield. However, in contrast to the site specificity we have observed in all other applications of this epoxidation reaction, we isolated in the present context two minor products **17** and **18**, which were shown by ^{1}H NMR and ^{13}C NMR to contain an *exo*-epoxide moiety at the norbornene end of the ring system. This was confirmed by an independent synthesis of **17** by treating the racemic mixture **12a**,**b** with *m*CPBA in dichloromethane. Although **17** and **18** were only minor products the formation of norbornane epoxides of this type was totally unexpected and, whilst electron deficient 7-oxanorbornene derivatives are known to react with the nucleophilic *tert*-butylhydroperoxide anion,[3c] this appeared to the first case of such a reaction occurring with a methylene bridged norbornene. Subsequent studies have suggested that the these epoxides are not derived from ^{t}BuOOH but are artefacts of the *aerial* oxidation of **12** and **16**. Subsequently we have found all similar cyclobutene ester amides are vulnerable and further investigation is currently underway to elucidate this unusual phenomenon.

We next addressed the task of exploiting these desymmetrised BLOCKS to construct edge functionalised [*n*]polynorbornanes. Three strategies exist for this problem (Scheme 5). The first is to build a framework *e.g.* **7** and then selectively attach the peptide chains (Path A). However, this sequence involves a repetitive de-esterification/re-esterification/de-esterification sequence. The second approach is to have all peptide chains in place prior to ACE reaction (Path B). This strategy is marred by the fact that bis amide substituted epoxides (*e.g.* **15**) undergo thermal ring opening at temperatures in excess of 160°. From our present study it was clear the epoxides substituted with both an ester and an amide behaved more normally with regard to thermal ring opening and underwent the ACE reaction at temperatures in the range 135–140°. Consequently, the most attractive strategy with respect to both efficiency and milder reaction conditions appeared to be one in which part of one peptide chain was in place prior to formation of the framework (Path C). Accordingly, we evaluated the reactions outlined in Scheme 6.

‡ The general concept of BLOCKs and their role in molecular architecture is described in reference 3(*a*).



Scheme 5 Strategies for edge functionalisation.



Scheme 6 ACE coupling and elaboration. *Reagents and conditions*: (i) sealed tube, norbornadiene, 130 °C. (ii) NaCN, DMF, *etc*. (iii) DiPCDI, amino acid ester, DMF, 12 h.

As anticipated, cycloaddition of the epoxide **19** with norbornadiene afforded the [3]polynorbornane framework **20** in good yield. However, all attempts to saponify the remaining methyl ester in adduct **20** with dilute NaOH failed. Nevertheless, the monoacid **21** was sucessfully prepared, by nucleophilic displacement using NaCN in DMF.[8]

Despite this success the resulting carboxylic acid **21** resisted all attempts to couple it with alanine methyl ester or for that matter any other suitably protected amino acid. Whilst the reason for this lack of reactivity is not clear it is presumably steric in origin and indicates that this approach to mixed amide edge substituted [*n*]polynorbornanes is at best likely to be fickle in the final stage. This finding also casts further doubt on path A in which synthesis might be sensitive to steric constraints. We therefore conclude that the most acceptable route to peptide substituted RAFTS is one involving bis amide epoxides *e.g.* **15**. These we have demonstrated can be synthesised from suitable epoxides and reacted with norbornenes, albeit at high temperature. In this context we are presently investigating elaboration of peptides using a short one or two amino acid spacer suitable for manipulation post ACE reaction.

In conclusion we have demonstrated that partial hydrolysis of dimethyl esters as described by Niwayama provides access to unlike edge substituted frameworks with ester/ester, amide/ester and acid/amide functionality. Furthermore, alkene groups suitable for further elaboration have been included making this style of polynorbornane an excellent RAFT. It is also pleasing to note that the judicious application of partial ester hydrolysis provides yet another entry to chiral BLOCKS and molecules derived from them.

Experimental

NMR spectra were recorded on a Varian Unity Plus 300 MHz spectrometer. Coupling constants (*J*) are given in Hz. Electrospray mass spectra (ES) were obtained with a platform II single quadropole mass spectrometer (Micromass, Altrincham, UK). High resolution mass spectra (HRMS) were measured by the Centre for Molecular Architecture, Central Queensland University, Rockhampton. Melting points were determined on a Reichart hotstage microscope and are uncorrected. Optical rotations were measured on a Jasco DIP-1000 digital polarimeter using the Na D line (589 nm) and 95% EtOH as solvent. Thin layer chromatography was performed on Merck Kieselgel 60 F_{254} plates. Column chromatography was performed using Merck Kieselgel 60 (70–230 mesh). All chromatography solvents were AR grade. Dichloromethane was distilled from CaH_2 and either used fresh or stored over 4 Å sieves. Anhydrous dimethylformamide was purchased from Aldrich Chemical Co. Tetrahydrofuran was freshly distilled from Na–benzophenone ketyl.

Starting materials

The diester **5** was synthesised by Mitsudo reaction from norbornene and dimethyl acetylenedicarboxylate (DMAD),[5] whilst alkene diester **8** was synthesised from quadricyclane and DMAD.[9] The epoxide **10** was synthesised from alkene **8** using our modification[1] of the ^{t}BuOOH–base reaction originally published by Meth-Cohn.[10]

General epoxidation procedure

A solution of alkene (1.0 equiv.) dissolved in freshly distilled THF (~10 ml per 100 mg substrate) under argon was cooled to 0 °C whereupon ^{t}BuOOH (3.04 M in toluene,[11] 1.5 equiv.) was added with stirring. The cold bath was maintained and after 10 mins ^{t}BuOK (0.3–0.5 equiv.) was added in one portion. A slight yellow to orange colour indicated that the reaction had commenced. When TLC monitoring indicated the reaction was complete (4–12 h) the reaction was quenched by addition of 10% Na_2SO_3 (1.5 equiv.) and the reaction stirred a further 10 min. This mix was subsequently partitioned between dichloromethane–H_2O (or chloroform–H_2O) and the organic phase separated. The aqueous phase was extracted twice more with dichloromethane (or chloroform) and the combined organic layers dried (Na_2SO_4), filtered and evaporated. Depending on the purity obtained the product was either subjected to chromatography (EtOAc–hexane) and/or recrystallised (EtOAc–hexane).

(1α,2β,5β,6α)-4-Methoxycarbonyl-tricyclo[4.2.1.0^{2,5}]non-3-ene-3-carboxylic acid 6

The alkene diester **5** (370 mg, 1.56 mmol) was dissolved in THF (2.5 ml) then slowly diluted with water (25 ml) with stirring. This solution was cooled to 0 °C in an ice bath then 0.25 M NaOH (20 ml) was added dropwise over a 30 min period with rapid stirring. The reaction was stirred for a further 30 min, after which TLC analysis revealed complete consumption of starting material and the cold reaction mixture was acidified with 10% HCl. This solution was extracted thoroughly with EtOAc and the combined organic extracts were dried (Na_2SO_4), filtered and evaporated to provide a crystalline solid. Yield 273 mg (78%). If further purification was required, the material could be recrystallised from EtOAc–hexane or subjected to column chromatography using EtOAc as eluent (R_f = 0.40); mp 121–123 °C (sublm. 105 °C); (Found: C 64.68, H 6.21. $C_{12}H_{14}O_4$ requires: C 64.85, H 6.35); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.05–1.18 (4H, m, H9*syn*,H9*anti*,H7,H8), 1.56–1.62 (2H, m, H7,H8), 2.19 (1H, s, H1,6), 2.29 (1H, s, H1,6), 2.68 (1H, d, *J* 3.4, H2,5), 2.75 (1H, d, *J* 3.4, H2,5), 3.87 (3H, s, CO_2Me); δ_C(300 MHz; $CDCl_3$) 27.51, 27.63, 30.31, 33.17, 33.26, 46.30, 47.62, 53.23, 141.45, 149.53, 160.47, 165.05.

(1α,2β,5β,6α)-4-Methoxycarbonyl-tricyclo[4.2.1.0^{2,5}]nona-3,7-diene-3-carboxylic acid 9

The alkene diester **8** (312 mg, 1.3 mmol) was treated as above. It was found that less 0.25 M NaOH (15.0 ml) was required to effect total mono-saponification. Yield of white crystals 270 mg (92%); (R_f = 0.45); mp 101–103 °C; (Found: C 65.25, H 5.51. $C_{12}H_{12}O_4$ requires: C 65.44, H 5.49); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.23 (1H, d, *J* 10.5, H9*syn*), 1.46 (1H, d, *J* 10.0, H9*anti*), 2.62 (1H, s, H) 2.69–2.71 (2H, m, H), 2.81 (1H, s, H), 3.93 (3H, s, CO_2Me), 6.20–6.25 (2H, m, H7,H8); δ_C(300 MHz; $CDCl_3$) 37.78, 37.86, 39.59, 43.57, 45.00, 53.35, 135.86, 136.35, 144.26, 153.08, 160.21, 165.16.

(1α,2β,5β,6α)-5-Methoxycarbonyl-4-oxatricyclo[5.2.1.02,6.0^{3,5}]-dec-8-ene-3-carboxylic acid 11

The diester epoxide **10** (59 mg, 0.27 mmol) was dissolved in THF (1.0 ml) and H_2O (7.5 ml) and treated with 0.25 M NaOH

(3.0 ml) as above. Yield of white crystals 30 mg (54%); mp > 350 °C (decomp.) (crystals developed a brown tinge at 240 °C which deepened as the temperature was increased); (Found: C 59.82, H 4.95. $C_{12}H_{12}O_5$ requires: C 61.01, H 5.13); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.42 (1H, d, *J* 9.0, H10), 1.81 (1H d, *J* 8.7, H10), 2.03 (1H, s, H6), 2.18 (1H, s, H2), 3.15 (1H, s, H7), 3.41 (1H, s, H1), 3.84 (3H, s, CO_2Me), 6.09–6.11 (2H, m, H8,H9); δ_C(300 MHz; $CDCl_3$): 41.71, 41.86, 41.93, 47.81, 48.88, 53.39, 66.89, 70.88, 137.14, 138.02, 167.44, 167.92.

3-Benzyl 4-methyl (1α,2β,5β,6α)-tricyclo[4.2.1.$0^{2,5}$]non-3-ene-3,4-dicarboxylate 3 (R=Bn)

To a cooled (0 °C), nitrogen-flushed, solution of the acid **6** (70 mg, 0.32 mmol) and dry benzyl alcohol (0.65 ml, 0.63 mmol) in dry dichloromethane (10.0 ml) the following reagents were added: diisopropylcarbodiimide (0.125 ml, 0.79 mmol) and dimethylaminopyridine (10 mg, 0.08 mmol).[12] The reaction mixture was allowed to stir at room temperature overnight whereupon it was transferred to a separatory funnel, diluted with dichloromethane (40 ml) and washed with water (30 ml). The organic phase was collected and the aqueous phase re-extracted with a second portion of dichloromethane (40 ml). The combined organic phases were dried (Na_2SO_4), filtered and evaporated to afford a crude product that, when subjected to column chromatography (3:7 EtOAc–hexane, R_f = 0.55), provided 66 mg (67%) of the title compound as a slightly viscous oil; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.06–1.16 (3H, m, H7,H8,H9), 1.35 (1H, d, *J* 9.8, H9), 1.58–1.64 (2H, m, H7,H8), 2.26 (2H, s, H2,H5), 2.69 (2H, s, H1,H6), 3.72 (3H, s, CO_2Me), 5.22 (2H, s, C*H*$_2$Ph), 7.27–7.41 (5H, m, CH_2*Ph*); δ_C(300 MHz; $CDCl_3$) 27.79, 30.36, 33.77, 47.31, 47.35, 51.67, 66.37, 127.99, 128.15, 128.48, 135.57, 141.84, 142.47, 160.94, 161.66, 161.65.

1-Benzyl 8-methyl (1α,2β,3α,6α,7β,8α,9β,10α,13α,14β)-16-oxahexacyclo[6.6.1.1^{3,6}.1^{10,13}.0^{2,7}.0^{9,14}]heptadecane-1,8-dicarboxylate 7 (R=Bn)

The epoxide **4** was prepared in the standard manner (see the general procedure) from the ester **3** and reacted immediately as described below. The epoxide **4** (13 mg, 0.040 mmol), norbornene (15 mg, 0.16 mmol) and dichloromethane (0.4 ml) were combined in a sealed tube under nitrogen. The tube was then heated at 140 °C for 10 h, after which it was cooled and cracked and the solvent evaporated to provide a crude product. This material was subjected to column chromatography using 1:6 EtOAc–hexane as the eluent and a single fraction was collected (R_f = 0.2). This fraction was evaporated to provide 14 mg (81%) of the title compound as a white solid that could be further purified by recrystallisation from EtOAc–hexane to yield colourless needles; mp 170–171 °C (sublm. 164 °C); (Found: C 73.8, H 6.9. $C_{26}H_{30}O_5$ requires: C 73.9, H, 7.1); δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.78 (2H, d, *J* 10.0, H15,H17), 1.03–1.06 (4H, m, H4,H5,H11,H12), 1.31–1.38 (4H, m, H4,H5,H11,H12), 1.94 (2H, s, H6,H10), 2.03 (2H, s, H3,H13), 2.04 (4H, s, H2,H7,H9,H14), 2.11 (2H, d, *J* 10.0, H15,H17), 3.83 (3H, s, CO_2Me), 5.30 (2H, s, C*H*$_2$Ph), 7.33–7.43 (5H, m, CH_2*Ph*); δ_C(300 MHz; $CDCl_3$) 28.76, 28.82, 33.89, 38.04, 38.18, 51.86, 55.72, 55.75, 66.37, 90.28, 90.45, 128.24, 128.35, 128.44, 135.79, 169.49, 170.19.

Methyl (1α,2β,5β,6α)-4-[(methoxycarbonyl)methylcarbamoyl]-tricyclo[4.2.1.$0^{2,5}$]nona-3,7-diene-3-carboxylate 12a,b

To a cooled nitrogen-flushed suspension of **9** (140 mg, 0.64 mmol), glycine methyl ester hydrochloride (200 mg, 1.6 mmol) and triethylamine (0.22 ml, 1.6 mmol) in dry dichloromethane (20.0 ml), the following reagents were added: diisopropylcarbodiimide (0.30 ml, 2.0 mmol) and dimethylaminopyridine (10 mg, 0.08 mmol). The reaction mixture was allowed to stir at room temperature overnight whereupon it was transferred to a separatory funnel, diluted with dichloromethane (40 ml) and washed with dilute citric acid (30 ml). The organic phase was collected and the aqueous phase re-extracted with a second portion of dichloromethane (40 ml). The combined organic extracts were dried (Na_2SO_4), filtered and evaporated to afford a crude product that, when subjected to column chromatography (3:7 EtOAc–hexane, R_f = 0.25) provided 122 mg (66%) of the title compound as a slightly viscous oil; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.22 (1H, d, *J* 9.5, H9), 1.35 (1H, d, *J* 9.7, H9), 2.50 (1H, d, *J* 2.2, H2), 2.59 (1H, d, *J* 2.2, H5), 2.63 (1H, s, H1), 2.75 (1H, s, H6), 3.74 (3H, s, CO_2Me), 3.83 (3H, s, CO_2Me), 4.09 (1H, dd, *J* 18.1, *J* 5.2, NHC*H*$_a$H$_b$CO$_2$Me), 4.16 (1H, dd, *J* 18.0, *J* 5.2, NHCH$_a$-*H*$_b$CO$_2$Me), 6.14–6.20 (2H, m, H7,H8), 9.27 (1H, br t, NH); δ_C(300 MHz; $CDCl_3$) 37.92, 38.13, 39.49, 41.15, 42.88, 43.82, 52.24, 52.29, 135.67, 136.21, 139.59, 153.43, 160.69, 163.49, 169.94; *m*/*z* (ES) 314.1 [$C_{15}H_{17}NO_5$ + Na]$^+$; Found 314.1007, [$C_{15}H_{17}NO_5$ + Na]$^+$ requires 314.1004.

Diastereomers of methyl (1α,2β,5β,6α)-4-[1-(benzyloxycarbonyl)-2-methylpropylcarbamoyl]tricyclo[4.2.1.$0^{2,5}$]nona-3,7-diene-3-carboxylate 13a,b

This was prepared following the procedure outlined above using **9** (80 mg, 0.36 mmol), (*S*)-valine benzyl ester hydrochloride (180 mg, 0.73 mmol), triethylamine (0.10 ml, 0.73 mmol), dichloromethane (10.0 ml), diisopropylcarbodiimide (0.25 ml, 1.7 mmol) and dimethylaminopyridine (5 mg, 0.04 mmol). Purification by means of column chromatography (3:7 EtOAc–hexane, R_f = 0.25) provided the valine amide (126 mg, 84%) as an extremely viscous oil. Small quantities of each diastereomer were obtained by means of careful chromatography (silica 230–400 mesh, 1:20 EtOAc–hexane) and combining only the front (**D1**) and tail (**D2**) of the relevant fractions.

D1: δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.97 {6H, dd, *J* 6.6, *J* 5.6, NCH[CH(C*H*$_3$)$_2$]CO$_2$Bn}, 1.24 (1H, d, *J* 9.7, H9), 1.36 (1H, d, *J* 9.6, H9), 2.29 {1H, m, NCH[C*H*(CH$_3$)$_2$]CO$_2$Bn}, 2.54 (1H, d, *J* 3.6, H5), 2.62 (1H, d, *J* 3.7, H2), 2.66 (1H, s, H6), 2.78 (1H, s, H1), 3.85 (3H, s, CO_2Me), 4.68 {1H, dd, *J* 8.6, *J* 4.6, NC*H*-[CH(CH$_3$)$_2$]CO$_2$Bn}, 5.13 (d, *J* 12.5, CO$_2$C*H*$_a$H$_b$Ph), 5.24 (d, *J* 12.5, CO$_2$CH$_a$*H*$_b$Ph), 6.17–6.21 (2H, m, H7,H8), 7.28–7.37 (5H, m, CO$_2$CH$_a$H$_b$*Ph*), 9.31 (1H, d, *J* 8.6, NH); δ_C(300 MHz; $CDCl_3$) 17.55, 19.16, 31.16, 38.05, 38.25, 39.63, 42.95, 44.01, 52.37, 57.38, 66.84, 128.23, 128.49, 135.53, 135.79, 136.34, 139.45, 153.92, 160.68, 163.55, 171.44; *m*/*z* (ES) 432.2 [$C_{24}H_{27}NO_5$ + Na]$^+$.

D2: δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.98 {6H, dd, *J* 6.8, *J* 2.4, NCH[CH(C*H*$_3$)$_2$]CO$_2$Bn}, 1.24 (1H, d, *J* 10.7, H9), 1.39 (1H, d, *J* 10.6, H9), 2.29 {1H, m, NCH[C*H*(CH$_3$)$_2$]CO$_2$Bn}, 2.53 (1H, d, *J* 3.6, H5), 2.62 (1H, d, *J* 3.7, H2), 2.66 (1H, s, H6), 2.80 (1H, s, H1), 3.85 (3H, s, CO_2Me), 4.62 {1H, dd, *J* 8.3, *J* 4.9, NC*H*-[CH(CH$_3$)$_2$]CO$_2$Bn}, 5.15 (d, *J* 12.2, CO$_2$C*H*$_a$H$_b$Ph), 5.22 (d, *J* 12.2, CO$_2$CH$_a$*H*$_b$Ph), 6.17–6.21 (2H, m, H7,H8), 7.28–7.38 (5H, m, CO$_2$CH$_a$H$_b$*Ph*), 9.27 (1H, d, *J* 8.3, NH); δ_C(300 MHz; $CDCl_3$) 17.66, 19.11, 30.90, 38.00, 38.19, 39.61, 42.86, 43.90, 52.35, 57.51, 66.82, 128.22, 128.26, 135.50, 135.73, 136.30, 139.41, 153.89, 160.66, 163.55, 171.44; *m*/*z* (ES) 432.2 [$C_{24}H_{27}NO_5$ + Na]$^+$.

Methyl (1α,2β,6β,7α)-5-[(methoxycarbonyl)methylcarbamoyl]-4-oxatetracyclo[5.2.1.$0^{2,6}$.$0^{3,5}$]dec-8-ene-3-carboxylate 16

Synthesis of this material was accomplished by epoxidation of **12a**,**b**; however, the degree of conversion was variable and the R_f of the starting material and product were identical which complicated isolation of the desired product. A more satisfactory route to the product commenced with the epoxide **11** following the procedure outlined for the preparation of **12a**,**b**. Using **11** (40 mg, 0.17 mmol), glycine methyl ester hydrochloride (42 mg, 0.33 mmol), triethylamine (0.050 ml, 0.36

mmol), dichloromethane (20.0 ml), DMF (1.0 ml), diisopropylcarbodiimide (0.070 ml, 0.45 mmol) and dimethylaminopyridine (5 mg, 0.04 mmol) and a reaction time of 48 h, afforded a crude product that, when subjected to column chromatography (3:7 EtOAc–hexane, R_f = 0.25), provided 29 mg (56%) of the title compound as a colourless, slightly viscous, oil; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.52 (1H, dt, *J* 9.7, *J* 1.2, H9), 1.74 (1H, d, *J* 9.9, H9), 2.25 (1H, dt, *J* 4.2, *J* 1.1, H2), 2.29 (1H, dt, *J* 4.2, *J* 1.1, H6), 3.23 (1H, s, H1), 3.44 (1H, s, H7), 3.75 (3H, s, CO_2Me), 3.85 (3H, s, CO_2Me), 3.97 (1H, dd, *J* 18.3, *J* 6.2, $NHCH_aH_bCO_2Me$), 4.11 (1H, dd, *J* 18.3, *J* 6.2, $NHCH_aH_bCO_2Me$), 6.15 (1H, dd, *J* 5.5, *J* 3.4, H7), 6.19 (1H, dd, *J* 5.5, *J* 3.4, H8); δ_C(300 MHz; $CDCl_3$) 40.74, 41.62, 41.69, 41.80, 48.20, 48.79, 52.38, 52.92, 67.28, 68.23, 137.21, 137.94, 164.18, 165.62, 169.45.

Methyl (1α,2β,5β,6α,7β,9β)-4-[(methoxycarbonyl)-methylcarbamoyl]-8-oxatetracyclo[4.3.1.0^{2,5}.0^{7,9}]dec-3-ene-3-carboxylate 17

This was obtained as a by-product from the epoxidation of **12a**,**b**; δ_H(300 MHz; $CDCl_3$; Me_4Si) 0.89 (1H, d, *J* 11.2, H10), 1.31 (1H, d, *J* 11.2, H10), 2.53 (1H, s, H1), 2.66 (1H, s, H6), 2.83 (1H, d, *J* 3.4, H2), 2.92 (1H, d, *J* 3.4, H5), 3.19–3.22 (2H, m, H7,H9), 3.78 (3H, s, CO_2Me), 3.85 (3H, s, CO_2Me), 4.09 (1H, dd, *J* 18.5, *J* 5.4, $NHCH_aH_bCO_2Me$), 4.17 (1H, dd, *J* 18.5, *J* 5.1, $NHCH_aH_bCO_2Me$), 9.26 (1H, br t, NH); δ_C(300 MHz; $CDCl_3$) 18.38, 34.49, 34.60, 41.21, 42.98, 43.93, 51.20, 51.23, 52.40, 52.54, 136.71, 150.73, 160.24, 163.00, 169.93; *m*/*z* (ES) 330.0 $[C_{15}H_{17}NO_6 + Na]^+$.

Methyl (1α,2β,6β,7α,8β,10β)-5-[(methoxycarbonyl)methylcarbamoyl]-4,9-dioxapentacyclo[5.3.1.0^{2,6}.0^{3,5}.0^{8,10}]undecane-3-carboxylate 18

This was obtained as a by-product from the epoxidation of **12a**,**b**; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.24 (1H, d, *J* 10.9, H12), 1.46 (1H, d, *J* 10.5, H12), 2.40 (1H, d, *J* 3.9, H2), 2.44 (1H, d, *J* 3.9, H6), 3.00 (1H, s, H1), 3.09 (2H, s, H8,H10), 3.22 (1H, s, H7), 3.75 (3H, s, CO_2Me), 3.84 (3H, s, CO_2Me), 3.95 (1H, dd, *J* 18.3, *J* 5.4, $NHCH_aH_bCO_2Me$), 4.08 (1H, dd, *J* 18.3, *J* 5.8, $NHCH_aH_bCO_2Me$), 6.92 (1H, br t, NH); δ_C(300 MHz; $CDCl_3$) 20.38, 36.85, 37.02, 40.71, 46.94, 47.60, 50.55, 50.69, 52.42, 52.09, 66.16, 67.08, 163.61, 165.02, 169.35; *m*/*z* (ES) 346.1 $[C_{15}H_{17}NO_7 + Na]^+$; Found 346.0906, $[C_{15}H_{17}NO_7 + Na]^+$ requires 346.0903.

Methyl (1α,2β,6β,7α)-5-[(*tert*-butoxycarbonyl)methylcarbamoyl]-4-oxatetracyclo[5.2.1.0^{2,6}.0^{3,5}]dec-8-ene-3-carboxylate 19

This was prepared following the procedure outlined for **12a**,**b** using **9** (200 mg, 0.9 mmol) and glycine *tert*-butyl ester (171 mg, 1.4 mmol). Column chromatography (1:6 EtOAc–hexane) provided 3-*methyl* (1*α*,2*β*,5*β*,6*α*)-4-[(tert-*butoxycarbonyl*)-*methylcarbamoyl*]*tricyclo*[4.2.1.0^{2,5}]*nona*-3,7-*diene*-3-*carboxylate* as a colourless viscous oil. Yield 240 mg (79%); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.23 (1H, d, *J* 9.5, H9), 1.36 (1H, d, *J* 10.2, H9), 1.48 (9H, s, $CO_2{}^tBu$), 2.51 (1H, d, *J* 3.7, H5), 2.61 (1H, d, *J* 3.5, H2), 2.65 (1H, s, H6), 2.78 (1H, s, H1), 3.85 (3H, s, CO_2Me), 4.01 (1H, dd, *J* 18.5, *J* 5.1, $NCH_aH_bCO_2{}^tBu$), 4.08 (1H, dd, *J* 18.5, *J* 5.1, $NCH_aH_bCO_2{}^tBu$), 6.16–6.21 (2H, m, H7,H8), 9.22 (1H, br t, NH); δ_C(300 MHz; $CDCl_3$) 28.01, 37.99, 38.21, 39.54, 42.15, 42.86, 43.85, 52.36, 82.13, 135.73, 136.29, 139.37, 153.65, 160.60, 163.53, 168.61; *m*/*z* (ES) 334.2 $[C_{18}H_{23}NO_5 + H]^+$, 356.1 $[M + Na]^+$, 372.1 $[M + K]^+$.

Subsequent epoxidation of this material (46 mg, 0.14 mmol) with ^tBuOOH afforded, after chromatography (1:6 EtOAc–hexane), a colourless oil. Yield 34 mg (71%); δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.46 (9H, s, $CO_2{}^tBu$), 1.50 (1H, d, *J* 10.5, H10), 1.74 (1H, d, *J* 9.5, H10), 2.24 (1H, d, *J* 3.9, H6), 2.29 (1H, d, *J* 4.1, H2), 3.23 (1H, s, H7), 3.44 (1H, s, H1), 3.84 (3H, s, CO_2Me), 3.88 (1H, dd, *J* 18.3, *J* 5.1, $NCH_aH_bCO_2{}^tBu$), 3.97 (1H, dd, *J* 18.3, *J* 5.1, $NCH_aH_bCO_2{}^tBu$), 6.13–6.19 (2H, m, H8,H9), 6.96 (1H, br t, NH); δ_C(300 MHz; $CDCl_3$) 28.00, 41.60, 41.70, 41.78, 48.18, 48.83, 52.83, 67.23, 68.28, 82.21, 137.21, 137.92, 163.86, 165.63, 168.01.

Methyl (1α,2β,3α,6α,7β,8α,9β,10α,13α,14β)-8-[(*tert*-butoxycarbonyl)methylcarbamoyl]-16-oxahexacyclo[6.6.1.1^{3,6}.1^{10,13}.0^{2,7}.0^{9,14}]heptadeca-4,11-ene-1-carboxylate 20

The following compounds were combined in a sealed tube under nitrogen: epoxide **19** (34 mg, 0.097 mmol), norbornadiene (25 mg, 0.28 mmol) and dichloromethane (0.4 ml). The tube was heated at 140 °C for 4.5 h, after which it was cooled and cracked and the solvent evaporated to provide a crude product. This material was subjected to column chromatography (1:6 EtOAc–hexane) and a single fraction was collected (R_f = 0.25). This fraction was evaporated to provide 34 mg (78%) of the title compound as an oil which solidified upon standing; mp 164–166 °C; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.07 (2H, d, *J* 8.8, H15,H17), 1.48 (9H, s, $CO_2{}^tBu$), 2.10 (2H, d, *J* 6.4, H7,H9), 2.19 (2H, d, *J* 6.5, H2,H14), 2.31 (2H, d, *J* 8.8, H15,H17), 2.63 (2H, s, H6,H10), 2.81 (2H, s, H3,H13), 3.88 (3H, s, CO_2Me), 4.02 (2H, d, *J* 5.7, Gly), 6.12 (2H, dd, *J* 5.4, *J* 2.9, H5,H11), 6.16 (2H, dd, *J* 5.6, *J* 2.9, H4,H12), 6.86 (1H, t, *J* 5.6, NH); δ_C(300 MHz; $CDCl_3$) 28.05, 41.35, 42.10, 43.48, 43.85, 52.06, 54.37, 55.07, 82.08, 88.16, 88.41, 138.88, 139.96, 168.19, 169.38, 169.90; *m*/*z* (ES) 442.7 $[C_{25}H_{31}NO_6 + H]^+$, 464.5 $[M + Na]^+$, 480.5 $[M + K]^+$; Found 464.2053, $[C_{25}H_{31}NO_6 + Na]^+$ requires 464.2049.

(1α,2β,3α,6α,7β,8α,9β,10α,13α,14β)-8-[(*tert*-butoxycarbonyl)-methylcarbamoyl]-16-oxahexacyclo[6.6.1.1^{1,8}.1^{3,6}.1^{10,13}.0^{2,7}.0^{9,14}]-heptadeca-4,11-diene-1-carboxylic acid 21

A solution of vacuum dried NaCN (45 mg, 0.92 mmol) in dry DMF (6.0 ml) was heated to 75 °C under nitrogen. To this, a solution of methyl ester **20** (61 mg, 0.14 mmol) in dry DMF (3.0 ml) was added and the reaction mixture stirred at 75 °C for 24 h. Work-up consisted of removal of the solvent under high vacuum and partitioning the residue between ether–water (50:50, 50 ml). The aqueous layer was separated and acidified to pH 4 with saturated citric acid. This was then extracted repeatedly with EtOAc, and the combined organic extracts were dried, filtered and evaporated to provide 27 mg (42%) of the desired acid; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.11 (2H, d, *J* 9.2, H15,H17), 1.49 (9H, s, $CO_2{}^tBu$), 2.17 (2H, d, *J* 6.7, H7,H9), 2.24 (2H, d, *J* 6.8, H2,H14), 2.30 (2H, d, *J* 9.2, H15,H17), 2.79 (2H, s, H6,H10), 2.82 (2H, s, H3,H13), 4.07 (2H, d, *J* 5.6, Gly), 6.15 (2H, dd, *J* 5.8, *J* 3.0, H5,H11), 6.18 (2H, dd, *J* 5.8, *J* 2.9, H4,H12), 7.00 (1H, t, *J* 5.5, NH); δ_C(300 MHz; $CDCl_3$) 28.06, 41.49, 42.13, 43.52, 43.79, 54.56, 55.05, 82.51, 88.05, 88.96, 138.98, 139.92, 168.48, 169.35, 172.11; *m*/*z* (ES) 450.3 $[C_{24}H_{29}NO_6 + Na]^+$.

References

1 G. V. Nikforvich, M. Mutter and C Lehman, *Biopolymers (Peptide Science)*, 1999, **50**, 361.

2 R. N. Warrener, D. N. Butler, D. Margetic, F. M. Pfeffer and R. A. Russell, *Tetrahedron Lett.*, 2000, **41**, 4671.

3 (*a*) R. N. Warrener, A. C. Schultz, D. N. Butler, S. Wang, I. Mahadaven and R. A. Russell, *J. Chem. Soc., Chem. Commun.*, 1997, 1023; (*b*) R. N. Warrener, D. N. Butler and R. A. Russell, *Synlett*, 1998, 566; (*c*) R. N. Warrener, D. Margetic, P. J. Foley, D. N. Butler, A. Winling, K. A. Beales and R. A. Russell, *Tetrahedron Lett.*, 2000, **51**, 571.

4 T. Mitsudo, H. Naruse, T. Kondo, Y. Ozaki and Y. Watanabe, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**(5), 580.

5 (*a*) R. A. Aitken, H. Hérion, A. Janosi, S. V. Raut, S. Seth, I. J. Shannon and F. C. Smith, *Tetrahedron Lett.*, 1993, **34**, 5621; (*b*) R. A. Aitken, H. Hérion, A. Janosi, N. Karodia, S. V. Raut, S. Seth, I. J. Shannon and F. C. Smith, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2467.

6 S. Niwayama, *J. Org. Chem.*, 2000, **65**, 5834.

7 All attempts to epoxidise such bis-amides have failed. See also

reference 2. We tentatively assign this to the acidic NH protons that are present in the substrate. This is supported by Meth-Cohn[10] where only traces of epoxide products were obtained from bis-amide alkenes.
8 (*a*) F. Elsinger, J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, 1960, **43**, 113; (*b*) P. Meuller and B. Seigfried, *Helv. Chim. Acta*, 1974, **57**, 987.
9 C. D. Smith, *J. Am. Chem. Soc.*, 1966, **88**, 4273.
10 O. Meth-Cohn, C. Moore and H. C. Taljaard, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2663.
11 B. K. Sharpless, B. Rossiter and G. Hill, *J. Org. Chem.*, 1983, **48**, 3607.
12 W. Steglich and B. Neises, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 522.