Synthesis of spirolactams via Diels-Alder addition of 1,3-butadienes to an α-methylene lactam

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(received 24 Sept 04; accepted 19 Oct 04; published on the web 02 Nov 04)

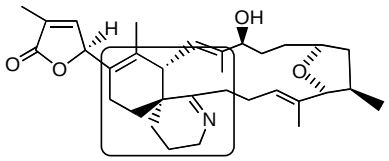
Abstract

As part of a programme directed towards the synthesis of the bicyclic spiroimine ring systems present in the marine toxins, the spirolides and gymnodimine, a study of the Diels-Alder addition of dienes **8**, **12,** cyclopentadiene and 2,3-dimethyl-1,3-butadiene to α-methylene lactam **7** was undertaken. A systematic study of the use of a variety of Lewis acids to catalyze the Diels-Alder reaction was undertaken. Extension of this work to an asymmetric variant of these Diels-Alder reactions was investigated using the chiral Lewis acids [(*S*,*S*)-^{t}Bu-BOX]Cu(OTf)$_2$ and [(*S*,*S*)-^{t}Bu-BOX]Cu(SbF$_6$)$_2$.

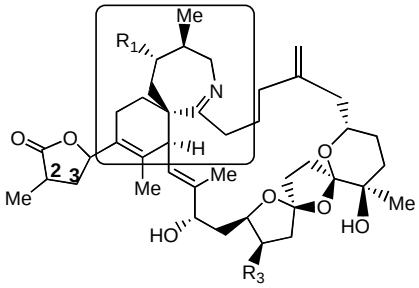
Keywords: α-Methylenelactams, Diels-Alder reaction, spirolactams, spirolides, gymnodimine

Introduction

Gymnodimine[1] **1** is a potent marine biotoxin[2] isolated from New Zealand oysters (*Tiostrea chilensis*) that exhibits neurotoxic effects in a mouse bioassay and contains an azaspiro[5.5]undecadiene subunit. This 6,6-spirocyclic ring system is also present in the fast acting toxin spiro-procentrimine[3] isolated from a Taiwanese laboratory-cultured *Procentrum* species. Macrocyclic toxins, spirolides A-D **2-5**,[4,5,6] isolated from the digestive glands of contaminated mussels (*Mytilus edulis*), scallops (*Placopecten magellanicus*) and toxic plankton from the eastern coast of Canada, contain a homologous 7,6-spirocylic imine ring system. This 7,6-spirocyclic imine ring system is also present in the related shellfish toxins, the pinnatoxins[7,8] and pteriatoxin.[9] The spirolides activate L-type calcium channels and act as muscarinic acetylcholine receptor antagonists, however, the related spirolides E and F[10] in which the spiromine unit was hydrolyzed, were found to be inactive. This observation together with the fact that gymnodamine in which the imine moiety is reduced, also resulted in a significant decrease in toxicity,[11] suggest the importance of this key structural feature on biological activity.



Gymnodimine **1**



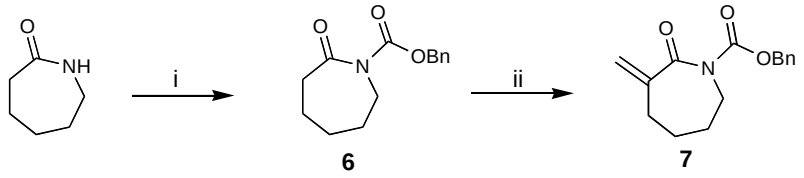
Spirolide A **2**; $\Delta_{2,3}$, R_1=H, R_2=Me
Spirolide B **3**; R_1=H, R_2=Me
Spirolide C **4**; $\Delta_{2,3}$, R_1=Me, R_2=Me
Spirolide D **5**; R_1=Me, R_2=Me

The mechanism of action of these imine-containing toxins was initially thought to involve covalent bond formation via nucleophilic addition to the imine, however Romo *et al.*[12] postulate that these α-quaternary substituted imines may serve as latent nucleophiles as a result of their masked enamine character as evidenced by their ability to completely incorporate deuterium at the exocyclic carbon after prolonged exposure to CD_3OD.

As part of a programme directed towards the synthesis of the spirolides,[13] we focused our attention on the synthesis of the unsubstituted spiromine units using a double alkylation – ring closing metathesis approach.[14] Difficulties adapting this strategy to the synthesis of more substituted systems prompted us to pursue an alternative approach to these heterocyclic frameworks via Diels-Alder addition of an appropriate diene to an α-methylene lactam. At the outset of this study the use of α-methylene lactams as dienophiles was rare,[15] however, during the course of this work several communications on the use of α-methylenelactams as dienophiles to construct spirolactams appeared in the literature.[16] We therefore herein report the full details of our preliminary work in this area and offer some improvements to the synthesis of the α-methylenelactam and diene starting materials. An aza-Wittig strategy is the only successful method that has been used to date to construct the spiroimine moiety in the total synthesis of the complex pinnatoxins.[17,18] White *et al.*[19] effected an intramolecular condensation of an amine to a silyl enol ether in their approach to the spiromine unit of gymnodimine after experiencing considerable difficulty in using a Diels-Alder strategy to construct the six membered ring.

Results and Discussion

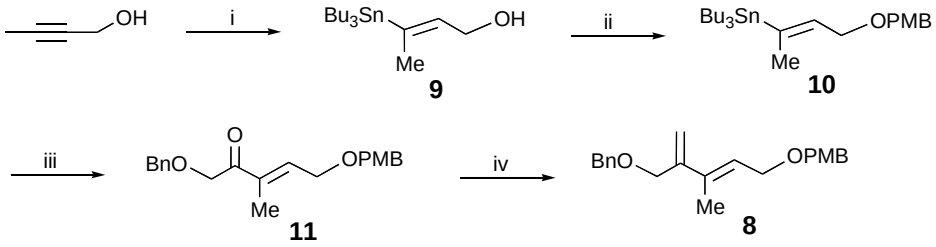
Treatment of caprolactam with butyl-lithium and benzyl chloroformate afforded CBz-protected caprolactam **6**[20] (Scheme 1) that was converted in one step to the seven membered α-methylene lactam **7** by treatment with LHMDS and Eschenmoser's salt followed by *in situ* methylation and elimination. This one step procedure was adapted from related work by Najera *et al.*[21] on the synthesis of five membered α-methylene lactams and offers an improvement on the four step conversion of CBz-protected caprolactam **6** to α-methylene lactam **7** reported in a communication by Murai *et al*.[16], that proceeds via a silyl ketene acetal intermediate.



Reagents and Conditions: (i) BuLi, CBzCl, THF, -78°C, 87%; (ii) LHMDS, $CH_2=NMe_2^+$ I^-, MeI, MeOH, room temp., 42%.

Scheme 1

Diene **8** was selected as the initial 4π component for the Diels-Alder reaction in that it contains two protected hydroxymethyl groups for further elaboration after construction of the spirolactam ring system. Our initial approach to diene **8** (Scheme 2) involved stannylcupration of 2-butyn-1-ol following the protocol developed by Piers,[22] affording (*E*)-vinylstannane **9** in 62% yield. Protection of the alcohol as a *p*-methoxybenzyl ether **10** followed by tin-lithium exchange and reaction of the resultant vinyl-lithium with the Weinreb amide derived from benzyloxyacetyl chloride afforded (*E*)-enone **11**. Subsequent Wittig olefination then provided the desired (*E*)-diene **8**. During the course of our work, White *et al*.[19] also reported a synthesis of vinyl stannane **10** via stannylcupration of ethyl 2-butynoate and its subsequent lithiation and reaction with a Weinreb amide.



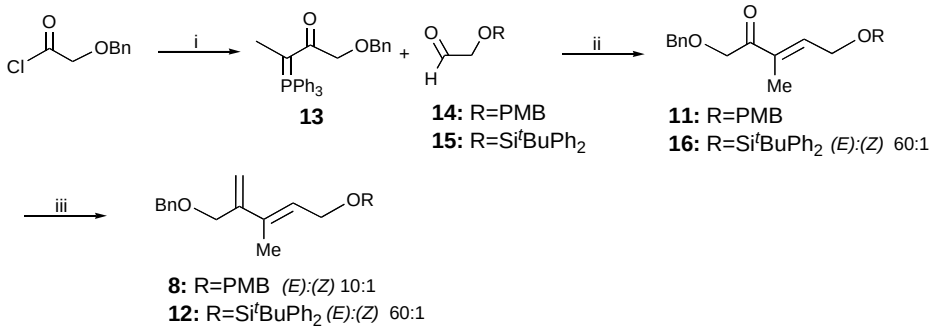
Reagents and Conditions: (i) $Bu_3Sn(Bu)CuCNLi_2$, -78°C, 62%; (ii) NaH, PMBCl, 61%; (iii) BuLi, THF, 78°C, $BnOCH_2CONMeOMe$, 42%; (iv) Ph_3P^+Me I^-, BuLi, 0°C, 35%.

Scheme 2

Difficulties associated with carrying out the stannylcupration on a large scale prompted us to investigate an alternative synthesis of diene **8** (Scheme 3). A better approach involved Wittig reaction of ylide **13** with either aldehyde **14** or **15** to afford enones **11** and **16** respectively, with high (*E*)-selectivity. Notably Wittig reaction using aldehyde **15** in which the hydroxyl group was protected as a bulky *tert*-butyldimethylsilylether, preceded with greater (*E*)-selectivity than the analogous reaction using *p*-methoxybenzyl protected aldehyde **14**. Ylide **13** was readily prepared by reaction of ethyltriphenylphosphonium bromide with butyl-lithium followed by addition of benzyloxyacetyl chloride. Reaction of ylide **13** with aldehyde **14** proceeded in high yield in dichloromethane at room temperature whereas aldehyde **15** required gentle refluxing conditions

to effect smooth reaction. Finally standard Wittig methylenation of enones **11** and **16** afforded dienes **8** and **12** respectively. A further advantage of this latter method is the elimination of the need to deal with toxic tin reagents.

Before investigating the asymmetric Diels-Alder addition of substituted 1,3-butadienes **8** and **12** to α-methylene lactams, we initially examined the addition of cyclopentadiene and 2,3-dimethyl-1,3-butadiene to α-methylene lactam **7** (Table 1). There was good literature precedent for high asymmetric induction using bidentate bis(oxazoline) BOX-copper (II) complexes in catalytic asymmetric Michael and Diels-Alder additions to substrates that can participate in catalyst chelation.[23] Extension of this idea to the use of benzyloxycarbonyl-protected α-methylene lactams seemed a logical step. Given that higher levels of asymmetric induction were observed[24] in Diels-Alder reactions catalyzed by BOX-copper (II) complexes when the non-coordinating hexafluoroantimonate counterion was used, both BOX-copper (II) triflate and hexafluoroantimonate complexes were evaluated in the present study. In the present work use of the hexafluoroantimonate complex resulted in loss of the *tert*-butyldimethylsilyl group when using diene **12**, thus prompting the parallel synthesis of the *p*-methoxybenzyl protected diene **8**.



Reagents and Conditions: (i) $Ph_3P^+Et\ Br^-$, BuLi, THF, 78°C, 53%; (ii) CH_2Cl_2, room temp., 24 h, **14**, 91%, reflux, 48h, **15**,95%; (iii) $Ph_3P^+Me\ I^-$, BuLi, 0°C, **8**, 40%, **12**, 92%.

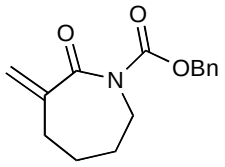
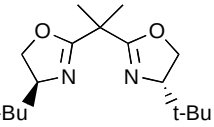
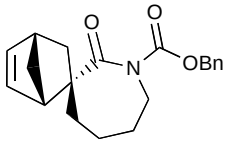
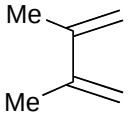
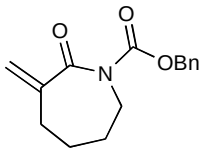
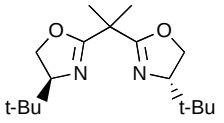
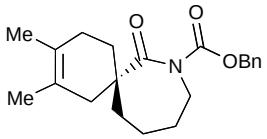
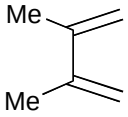
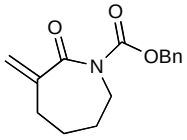
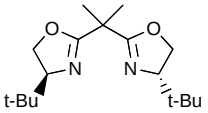
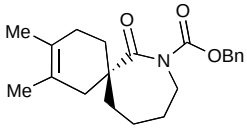
Scheme 3

The chiral BOX-copper (II) triflate complexes were formed by reacting [(*S*),(*S*)]-tBu-BOX] ligand with copper (II) triflate in dichloromethane at room temperature for 6 h giving a characteristically blue solution. The cationic hexafluoroantimonate complexes were prepared by anion exchange from the pre-formed copper (II) chloride complex using silver (I) hexafluoroantimonate, followed by filtration through Celite to remove the precipitated silver (I) chloride.

Addition of cyclopentadiene to α-methylenelactam **7** in dichloromethane at room temperature for 3 h in the presence of 20 mol% [(*S*,*S*)-^{t}Bu-BOX]Cu(OTf)$_2$ provided Diels-Alder adduct **17** in 53% yield as a 2:1 ratio of *exo*:*endo* isomers. This result was in agreement with a similar study by Murai *et al*.[16] in which the slight *exo*-selectivity (*exo*:*endo* 1.6:1) observed in Diels-Alder reactions using a conformationally rigid cyclic cisoid dienophile is accounted for by Berson's

dipole moment hypotheses.[25, 26] The enantiomeric excess was determined to be 58% by chiral HPLC on a Chiralpak™ ADH column using 99:1 hexane:^{i}PrOH at a flow rate of 0.3 mL/.

Table 1. Reaction of α-methylene lactam **7** with dienes using bis(oxazoline)-copper complexes

Entry	Diene	Dienophile	Conditions	Product[#]
1		 **7**	 $Cu(OTf)_2$ (20 mol%),CH_2Cl_2, room temp., 3 h	 **17** 53% yield, 2:1 *exo:endo* 58% e.e.
2		 **7**	 $Cu(OTf)_2$ (20 mol%),CH_2Cl_2, room temp., 24 h	 **18** 26% yield, 58% e.e.
3		 **7**	 $Cu(SbF_6)_2$ (20 mol%),CH_2Cl_2, room temp., 24 h	 **18** 30% yield, 94% e.e.

[#] Absolute configurations of the products have not been established.

The reaction of 2,3-dimethyl-1,3-butadiene with α-methylene lactam **7** was next investigated. In this case using 20 mol% [(*S*,*S*)-^{t}Bu-BOX]$Cu(OTf)_2$ the reaction proceeded sluggishly, with the desired adduct **18** isolated in only 26% yield after 24 h. The enantiomeric excess was also determined to be 58% by chiral HPLC using a Chiralpak™ ADH column.

Evans *et al*.[24] report that use of the SbF_6 complex accelerates copper (II)-BOX catalysed Diels-Alder reactions. Thus, in order to improve the yield and selectivity of the reaction of 2,3-dimethyl-1,3-butadiene with α-methylene lactam **7**, the SbF_6 complex was also investigated (entry 3). Disappointingly the SbF_6 complex afforded the adduct **18** in similar yield but with a significantly improved enantiomeric excess of 94%.

Use of substituted 1,3-butadienes **8** and **12** as the diene component in Diels-Alder reactions with α-methylene lactam **7** using both the [(*S*,*S*)-^{t}Bu-BOX]$Cu(OTf)_2$ and [(*S*,*S*)-^{t}Bu-BOX]-$Cu(SbF_6)_2$ catalysts proved fruitless in our hands with none of the desired adduct being observed. Expansion of the range of Lewis acid catalysts used to include Me_2AlCl, $LiClO_4$, $Sc(OTf)_3$, $Yb(OTf)_3$, albeit in an attempt to prepare racemic Diels-Alder adduct with diene **7**, proved equally unrewarding.

In summary the work reported herein focuses on the use of bis(oxazoline)-copper (II) complexes as chiral catalysts for the development of an asymmetric addition of 1,3-butadienes to α-methylenelactams. The results obtained indicate that the yields obtained in these reactions are

moderate thus redirecting our attention to an alternative strategy to construct the spiroimine unit of the spirolides and gymnodimine. Whilst our efforts in this area have proved disappointing, improved syntheses of α-methylene lactam **7** and dienes **8** and **12** with full experimental details, are reported herein together with full spectroscopic characterization of the spirolactams **17** and **18**.

Experimental Section

General Procedures. Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Optical rotations were determined on a Perkin-Elmer 341 polarimeter. Infrared spectra were recorded with a Perkin-Elmer 1600 series Fourier-transform infrared spectrometer as thin films between sodium chloride plates. ^{1}H and ^{13}C NMR spectra were recorded as indicated on either a Bruker AC200 spectrometer operating at 200 MHz for ^{1}H nuclei and 50 MHz for ^{13}C nuclei, a Bruker DRX300 spectrometer operating at 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei, or a Bruker DRX400 spectrometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. Both ^{1}H and ^{13}C NMR spectra were interpreted with the aid of COSY, HETCOR and DEPT 135 experiments and are reported in ppm downfield from tetramethylsilane as reference. High-resolution mass spectra were recorded using a VG 7070 spectrometer operating with an ionisation potential of 70 eV at a nominal resolution of 5000 or 10000 as appropriate. Major fragments are assigned where possible and their intensities given as percentages of the base peak. Tetrahydrofuran was dried using sodium/benzophenone and distilled prior to use. Flash chromatography was performed using either Merck Kieselgel 60 or Riedel-de-Haën Kieselgel S silica gel (both 230-400 mesh), or Merck aluminium oxide (70-230 mesh), with the indicated solvents. Compounds were visualized under ultraviolet light or by staining with iodine vapour or with vanillin in methanolic sulfuric acid.

Benzyl 2-oxo-1-azepanecarboxylate (6).[16,20] To a solution of ε-caprolactam (3.63 g, 32.0 mmol) in THF (70 mL) at –78 °C was added *n*-BuLi (1.6 M, 32 mmol). The reaction mixture was stirred at –78 °C for 30 min. Benzyl chloroformate (41.0 mmol, 5.85 mL) was then added and the resulting mixture stirred at –78 °C for 1 h. The resulting mixture was warmed to room temperature, quenched with water (20 mL) and extracted with ethyl acetate (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. The residue was purified by flash chromatography (hexane/ethyl acetate 2:1) to give the *title compound* **6** (3.34 g, 87%) as a pale yellow oil. δ_H (300 MHz; $CDCl_3$) 1.74–1.78 (6H, m, 4-, 5-, 6-C*H*$_2$), 2.66–2.69 (2H, m, 3-C*H*$_2$), 3.83–3.86 (2H, m, 7-C*H*$_2$), 5.28 (2H, s, 1'-C*H*$_2$), 7.26–7.44 (5H, m, 2"- to 6"-C*H*); δ_C (100 MHz; $CDCl_3$) 23.5 (*C*H$_2$, C-4), 28.6 (*C*H$_2$, C-6), 29.1 (*C*H$_2$, C-5), 39.4 (*C*H$_2$, C-3), 46.4 (*C*H$_2$, C-2), 68.5 (*C*H$_2$, C-1'), 127.9 (*C*H, C-2" and C-6"), 128.2 (*C*H, C-4"), 128.5 (*C*H, C-3" and C-5"), 135.5 (quat, C-1"), 154.3 (quat, C=O, Cbz), 175.5 (quat, C-2).

Benzyl 3-methylene-2-oxo-1-azepanecarboxylate (7).[16] To a solution of benzyl-2-oxo-1-azepane-carboxylate (300 mg, 1.21 mmol) in THF (3 mL) at –78 °C was added a freshly prepared solution of LiHMDS (1.57 mmol). The mixture was stirred for 1 h and then transferred via cannula to a pre-cooled (–78 °C) suspension of Eschenmoser's salt (492 mg, 2.66 mmol) in THF (2 mL). The resulting mixture was stirred at –78 °C for 4 h and the temperature was then allowed to rise to room temperature. The resulting solution was quenched with sat. aqueous $NaHCO_3$ (10 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried with anhydrous $MgSO_4$ and the solvents removed *in vacuo*. The residue was dissolved in dry MeOH (10 mL) and an excess of MeI (5 mL) was added. The reaction was stirred at RT for 24 h and the solvent removed *in vacuo*. Sat. aqueous $NaHCO_3$ (40 mL) was added and the mixture extracted with ethyl acetate (2 x 20 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$), and the solvents removed *in vacuo*. The residue was purified by flash chromatography (hexane/ethyl acetate 4:1) to give the *title compound* **7** (136 mg, 42%) as a yellow oil. ν_{max} (NaCl)/cm^{-1} (neat) 3090-3033, 2936, 2859, 1765, 1710, 1453, 1379, 1339, 1263, 1013; δ_H (300 MHz, $CDCl_3$) 1.71–1.80 (4H, m, 5-, 6-C*H*$_2$), 2.40–2.44 (2H, m, 4-C*H*$_2$), 3.73–3.76 (2H, m, 7-C*H*$_2$), 5.29 (2H, s, 1'- C*H*$_2$), 5.43 (1H, d, *J* 1.2, 3A-*H*), 5.81 (1H, d, *J* 1.2, 3B-*H*), 7.30–7.45 (5H, m, 2"- to 6"-C*H*); δ_C (75 MHz, $CDCl_3$) 27.9 (*C*H$_2$, C-5), 29.0 (*C*H$_2$, C-6), 32.4 (*C*H$_2$, C-4), 46.3 (*C*H$_2$, C-7), 68.3 (*C*H$_2$, C-1'), 123.8 (*C*H$_2$, 3-*C*H$_2$), 127.7 (*C*H, C-2" and C-6"), 128.1 (*C*H, C-4"), 128.5 (*C*H, C-3" and C-5"), 135.6 (quat, C-1'), 146.7 (quat, C-3), 154.0 (quat, C=O, Cbz), 172.1 (quat, C-2); *m/z* (EI): 259 (M^+, 2.5%), 231 (M – C_2H_4, 28), 107 (M – $C_9H_{10}O_2$, 152) and 91 (100); HRMS (EI): Found M^+, 259.12063. $C_{15}H_{17}NO_3$ requires *M*, 259.12084.

(*E*)-3-(Tributylstannyl)-2-buten-1-ol (9). To a suspension of CuCN (18.7 mmol) in THF (25 mL) was added dropwise *n*-BuLi (2.16 M in hexane, 18.2 mL, 39.3 mmol) at –78 °C. The solution was stirred for 10 min at 0°C (pale yellow colour) then recooled to –78 °C. Tributyltin hydride (29.17 mmol, 7.85 ml) was added and the solution was stirred for 10 min (yellow gold colour) at –78 °C. A solution of 2-butyn-1-ol (0.534 mL, 7.13 mmol) in THF (5 mL) containing dry MeOH (0.491 mL, 12.12 mmol) was added dropwise to the cuprate reagent at –100 °C forming a red solution. The mixture was stirred for 15 min then allowed to warm to –78 °C and stirred for 3 h. Sat. aqueous NH_4Cl (30 mL) was added at –78 °C, the mixture stirred vigorously and allowed to warm to room temperature until the aqueous phase developed a deep blue colour. After extraction with diethyl ether (2 x 20 mL), the combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by flash chromatography (hexane/ether 5:1) provided the *title compound* **9** as a pale yellow oil (1.58 g, 62%). Spectroscopic data were in agreement with those reported in literature.[27]

4''-Methoxybenzyl (*E*)-3-(tributylstannyl)-2-butenyl ether (10). To a suspension of sodium hydride (60% in mineral oil, 88 mg, 3.66 mmol) in DMF (10 mL) was added (*E*)-3-(tributyl-stannyl)-2-buten-1-ol (1.1 g, 3.05 mmol) at 0 °C, and the reaction mixture stirred for 30 min. To this mixture was added *p*-methoxybenzyl chloride (0.5 mL, 3.66 mmol) and tetrabutyl-ammonium iodide (255 mg, 0.7 mmol) and the resultant mixture stirred for 18 h at room

temperature. The mixture was diluted with sat. aqueous NH_4Cl (30 mL) and extracted with diethyl ether (2 x 20 mL). The organic phase was washed with sat. aqueous NH_4Cl (30 mL), distilled water (2 x 20 mL), brine (20 mL) and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the residue was purified by column chromatography (hexane/ether 5:1) to furnish the *title compound* **10** (930 mg, 61%) as a colourless oil. Spectroscopic data were in agreement with those reported in literature.[19]

(*E*)-1-(Benzyloxy)-5-[(4''-methoxybenzyl)oxy]-3-methyl-3-penten-2-one (11). *n*-BuLi (1.36 M in hexane, 0.26 mL, 0.35 mmol) was added slowly at –78 °C to a stirred solution of 4''-methoxybenzyl (*E*)-3-(tributylstannyl)-2-butenyl ether (0.57 g, 1.18 mmol) in THF (3 mL). The mixture was stirred at –78°C for 20 min then *N*-methoxy-*N*-methyl-2-(benzyloxy)acetamide (86.6 mg, 0.414 mmol) in THF (2 mL) was added dropwise over 5 min. The solution was stirred at –78 °C for 15 min then allowed to warm to 25 °C. After stirring for 1 h, sat. aqueous NH_4Cl (20 mL) was added. The mixture was extracted with diethyl ether (2 x 20 mL) and the solution subsequently washed with 1 M KF (20 mL). The combined organic layers were dried ($MgSO_4$), and the solvent evaporated *in vacuo*. The residue was purified by column chromatography (hexane/ether 2:1) to provide the *title compound* **11** (18 mg, 42%) as a pale yellow oil. ν_{max} (NaCl)/cm^{-1} (CH_2Cl_2) 2985, 2928, 2859, 2305, 1687, 1612, 1550, 1513, 1421; δ_H (300 MHz; $CDCl_3$) 1.75 (3H, m, 3-CH_3), 3.80 (3H, s, OCH_3), 4.19 (2H, dd, $J_{5,4}$ 5.5 and $J_{5,3Me}$ 0.8, 5-CH_2), 4.46 (2H, s, 1-CH_2), 4.47 (2H, s, 1'-CH_2), 4.60 (2H, s, 1'''-CH_2), 6.58–6.62 (1H, m, 4-*H*), 6.88 (2H, d, *J* 8.6, 3''- and 5''-C*H*), 7.25 (2H, d, *J* 8.6, 2''- and 6''-C*H*), 7.34–7.36 (5H, m, 2''''- to 6''''-C*H*); δ_C (75 MHz; $CDCl_3$) 11.6 (*C*H_3, 3-CH_3), 55.3 (*C*H_3, O*C*H_3), 66.8 (*C*H_2, C-5), 71.6 (*C*H_2, C-1'), 72.8 (*C*H_2, C-1), 73.3 (*C*H_2, C-1'''), 113.9 (*C*H, C-3'' and C-5''), 127.9 (*C*H, C-4''''), 128.0 (*C*H, C-2'''' and C-6''''), 128.5 (*C*H, C-3'''' and C-5''''), 129.5 (CH, C-2'' and C-6''), 129.6 (quat, C-1''), 135.7 (quat, C-4''''), 137.4 (quat, C-3), 138.9 (*C*H, C-4), 159.4 (quat, C-4''), 196.9 (quat, C-2); *m/z* (DEI): 340 (M^+, 0.08%) and 121 (100); HRMS (EI): Found M^+, 340.16776. $C_{21}H_{24}O_4$, requires M^+, 340.16746.

Benzyl (*E*)-5-[(4''-methoxybenzyl)oxy]-3-methyl-2-methylene-3-pentenyl ether (8). (*E*)-1-(Ben-zyloxy)-5-[(4''-methoxybenzyl)oxy]-3-methyl-3-penten-2-one **11** (30 mg, 88 μmol) was dissolved in dry THF (10 mL) at room temperature and then cooled to 0°C. To this mixture was added methylenetriphenylphosphorane ylide[28] in THF (2.2 mL). The reaction mixture was stirred at 0°C for 1 h, quenched by the addition of sat. aqueous $NaHCO_3$ (20 mL) solution and extracted with ether (3 x 20 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate 9:1) to give the *title compound* **8** (10 mg, 35%) as a pale yellow oil; ν_{max} (NaCl)/cm^{-1} (neat) 2929, 2855, 1612, 1513, 1248, 1095, 1072, 1035; δ_H (400 MHz; $CDCl_3$) 1.81 (3H, m, 3-CH_3), 3.80 (3H, s, OCH_3), 4.12 (2H, d, $J_{5,4}$ 6.3, 5-CH_2), 4.22 (2H, s, 1-CH_2), 4.45 (2H, s, 1'-CH_2), 4.52 (2H, s, 1'''-CH_2), 5.25 (1H, bs, 2-C$H_a$$H_b$), 5.26 (1H, bs, 2-$CH_a$$H_b$), 5.82 (1H, t, $J_{4,5}$ 6.3, 4-*H*), 6.87 (2H, d, *J* 8.6, 3''- and 5''-C*H*), 7.26 (2H, d, *J* 8.6, 2''- and 6''-C*H*), 7.28–7.35 (5H, m, 2''''- to 6''''-C*H*); δ_C (100 MHz; $CDCl_3$) 14.5 (*C*H_3, 3-CH_3), 55.3 (*C*H_3, O*C*H_3), 66.8 (*C*H_2, C-5), 71.3 (*C*H_2, C-1'), 72.0 (*C*H_2, C-1), 72.2 (*C*H_2, C-1'''), 113.80 (*C*H, C-3'' and C-5''), 113.9 (*C*H_2, 2-CH_2), 124.5 (*C*H, C-4), 127.6

(*C*H, C-4""), 127.8 (*C*H, C-2"" and C-6""), 128.4 (*C*H, C-3"" and C-5""), 129.5 (CH, C-2" and C-6"), 130.4 (quat, C-1"), 135.5 (quat, C-4""), 138.4 (quat, C-3), 144.9 (quat, C-2), 159.2 (quat, C-4"); *m/z* (EI): 338 (M^+, 0.3%), 247 (M – C_7H_7, 91) and 121 (100); HRMS (EI): Found M^+, 338.18850 $C_{22}H_{26}O_3$, requires M^+, 338.18819.

1-(Benzyloxy)-3-(triphenyl-λ^5-phosphanylidene)-2-butanone (13). A solution of *n*-BuLi (1.6 M in hexane, 10.6 mL, 16.96 mmol) was added slowly to a stirred suspension of ethyltriphenylphosphonium bromide (6.3 g, 16.96 mmol) in THF (45 mL) at –78 °C producing an orange solution. The mixture was warmed to 0°C and stirred for 30 min. The ylide solution was then added dropwise via cannula to a solution of benzyloxyacetyl chloride (0.84 mL, 5.41 mmol) in THF (15 mL), which had been cooled to –78 °C. The reaction was maintained at –78 °C for 1 h, allowed to warm to room temperature for 2 h then quenched by the addition of sat. aqueous NH_4Cl (60 mL). The product was extracted with ethyl acetate (3 x 50 mL) and the organic phase washed with sat. aqueous $NaHCO_3$ (2 x 50 mL), brine (2 x 50 mL) and dried (Na_2SO_4). Concentration *in vacuo* gave a red oil, which was recrystallised from hexane/ethyl acetate (10:1) to give the *title compound* **13** (1.26 g, 53%) as a pale red amorphous solid. Mp 98-100°C, ν_{max} (NaCl)/cm^{-1} (CH_2Cl_2) 3062, 3030, 2924, 2249, 2225, 1520, 1483; δ_H (300 MHz, $CDCl_3$) 1.64 (3H, d, $J_{4,P}$ 16.1, C*H*$_3$), 4.28 (2H, s, 1-C*H*$_2$), 4.67 (2H, s, 1'-C*H*$_2$), 7.26-7.62 (20H, m, ArH); *m/z* (FAB): 439 (MH^+, 100%); HRMS (FAB): Found MH^+, 439.18304. $C_{29}H_{28}O_2P$, requires MH^+, 439.18269.

2-[(4''-Methoxybenzyl)oxy]acetaldehyde (14). To a stirred solution of oxalyl chloride (2.8 mL, 31.9 mmol) in CH_2Cl_2 (60 mL) at –78 °C was added dimethyl sulfoxide (2.8 mL, 39.1 mmol). After 15 min, a solution of (*p*-methoxybenzyloxy)ethanol (3 g, 16.6 mmol) in CH_2Cl_2 (20 mL) was added dropwise. The mixture was maintained at –78 °C for 20 min, then Et_3N (9.2 mL, 66.3 mmol) was added. After stirring for 5 min, the mixture was allowed to warm to room temperature over 1.5 h. Water (40 mL) was added and the resulting mixture washed with 1 M HCl (2 x 50 mL), sat. aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford the desired crude aldehyde. Purification by flash chromatography (hexane/ethyl acetate 5:1) yielded the *title compound* **14** (1.5 g, 50%) as a yellow oil. Spectroscopic data were in agreement with those reported in literature.[29]

***tert*-Butyldiphenylsilyloxyacetaldehyde (15).** To a stirred solution of oxalyl chloride (0.48 mL, 5.6 mmol) in CH_2Cl_2 (20 mL) at –78 °C was added dimethyl sulfoxide (0.48 mL, 6.8 mmol). After 15 min, a solution of 2-(*tert*-butyldiphenylsiloxy)ethanol (0.7 g, 2.88 mmol) in CH_2Cl_2 (10 mL) was then added dropwise. The mixture was maintained at –78 °C for 20 min then Et_3N (1.6 mL, 11.52 mmol) was added. After stirring for 5 min, the mixture was allowed to warm to room temperature over 1.5 h. Water (40 mL) was added and the resulting mixture washed with 1 M HCl (2 x 50 mL), sat. aqueous $NaHCO_3$ (20 mL) and brine (20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude aldehyde. Purification by flash chromatography (hexane/ethyl acetate 6:1) yielded the *title*

compound **15** (0.69 g, 82%) as a yellow oil. Spectroscopic data were in agreement with those reported in literature.[30]

(*E*)-1-(Benzyloxy)-5-[(4''-methoxybenzyl)oxy]-3-methyl-3-penten-2-one (11). To a solution of ylide **13** (2.60 g, 5.95 mmol) in CH_2Cl_2 (20 mL) was added aldehyde **14** (1 g, 5.95 mmol) and the mixture was stirred at room temperature for 24 h. Concentration *in vacuo* gave an orange/red oil that was purified by flash chromatography (hexane/ethyl acetate 9:1) to give the *title compound* **11** (1.84 g, 91%) as a light yellow oil for which the spectroscopic data were in agreement with those reported above.

(*E*)-1-(Benzyloxy)-5-[*tert*-butyl(diphenyl)silyl]oxy-3-methyl-3-penten-2-one (16). To a solution of ylide **13** (2.44 g, 5.57 mmol) in CH_2Cl_2 (20 mL) was added aldehyde **15** (600 mg. 2.01 mmol) and the mixture was heated at reflux for 48 h. Concentration *in vacuo* gave an orange/red oil that was purified by flash chromatography (hexane/ethyl acetate 9:1) to give the *title compound* **16** (875 mg, 95%) as a light yellow oil. ν_{max} (NaCl)/cm^{-1} (neat) 3070, 3030, 2930, 2857, 1690, 1671, 1472, 1428, 1112, 1055; δ_H (300 MHz, $CDCl_3$) 1.06 (9H, s, *t*-Bu), 1.57 (3H, s, 3-C*H*$_3$), 4.40-4.42 (2H, m, 5-C*H*$_2$), 4.41 (2H, s, 1-C*H*$_2$), 4.60 (2H, s, 1'-C*H*$_2$), 6.59 (1H, m, 4-*H*), 7.26–7.43 (11H, m, 2'''-, 4'''-, 6'''-C*H* and 1''- to 6''-C*H*), 7.64–7.67 (4H, m, 3'''- and 5'''-C*H*); δ_C (75 MHz, $CDCl_3$) 11.4 (*C*H$_3$, 3-CH$_3$), 26.8 (*C*H$_3$, *t*-Bu), 61.4 (*C*H$_2$, C-5), 71.7 (*C*H$_2$, C-1), 73.3 (*C*H$_2$, C-1'), 127.9 (*C*H, C-2''' and C-6'''), 127.9 (*C*H, C-4''), 128.0 (*C*H, C-2'' and C-6''), 128.5 (*C*H, C-3'' and C-5''), 129.9 (*C*H, C-4'''), 133.1 (quat, C-1'''), 134.1 (quat, C-1''), 135.5 (*C*H, C-3''' and C-5'''), 137.5 (quat, C-3), 141.9 (*C*H, C-4), 197.0 (quat, C-2); *m/z* (EI): 458 (M$^+$, 0.1%), 443 (M – CH$_3$, 15), 401 (M – C$_4$H$_9$, 57) and 91 (100); HRMS (EI): Found M$^+$, 458.22650. $C_{29}H_{34}O_3Si$, requires M$^+$, 458.22772.

Benzyl (*E*)-5-[*tert*-butyl(diphenyl)silyl]oxy-3-methyl-2-methylene-3-pentenyl ether (12). A solution of (*E*)-1-(benzyloxy)-5-[*tert*-butyl(diphenyl)silyl]oxy-3-methyl-3-penten-2-one **16** (434 mg, 0.95 mmol) in THF (5 mL) was cooled to 0°C. To this solution was added methylenetriphenylphosphorane ylide[28] in THF (10 mL). The reaction mixture was stirred at 0 °C for 1 h, quenched by the addition of sat. aqueous $NaHCO_3$ (20 mL) and extracted with diethyl ether (3 x 20 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (hexane/ether 8:1) to give the *title compound* **12** (397 mg, 92%) as a pale yellow oil. ν_{max} (NaCl)/cm^{-1} (neat) 3069, 2956, 2930, 2889, 2856, 1472, 1454, 1427, 1111, 1055; δ_H (300 MHz, $CDCl_3$) 1.05 (9H, s, *t*-Bu), 1.63 (3H, s, 3-C*H*$_3$), 4.19 (2H, s, 1-C*H*$_2$), 4.38 (2H, d, $J_{5,4}$ 5.9, 5-C*H*$_2$), 4.53 (2H, s, 1'-C*H*$_2$), 5.21 (1H, bs, 2-C*H*$_a$H$_b$), 5.23 (1H, bs, 2-CH$_a$*H*$_b$), 5.85 (1H, t, $J_{4,5}$ 5.9, 4-*H*), 7.26–7.43 (11H, m, 2'''-, 4'''-, 6'''-C*H* and 1''- to 6''-C*H*), 7.64–7.67 (4H, m, 3'''- and 5'''-C*H*); δ_C (75 MHz, $CDCl_3$) 14.3 (*C*H$_3$, 3-CH$_3$), 26.8 (*C*H$_3$, *t*-Bu), 61.6 (*C*H$_2$, C-5), 71.4 (*C*H$_2$, C-1), 72.2 (*C*H$_2$, C-1'), 113.5 (*C*H$_2$, 2-CH$_2$), 127.5 (*C*H, C-4''), 127.6 (*C*H, C-2''' and C-6'''), 127.7 (*C*H, C-2'' and C-6''), 127.7 (*C*H, C-4), 128.4 (*C*H, C-3'' and C-5''), 129.6 (*C*H, C-4'''), 132.9 (quat, C-1'''), 133.8 (quat, C-1''), 135.6 (*C*H, C-3''' and C-5'''), 138.4 (quat, C-3), 144.0 (quat, C-2); *m/z* (EI): 456 (M$^+$, 0.1%), 399 (M – C$_4$H$_9$, 57) and 91 (100); HRMS (EI): Found M$^+$, 456.24812. $C_{30}H_{36}O_2Si$, requires M$^+$, 456.24846.

Spiro[bicyclo[2.2.1]hept-5-ene-2,3'-azepan]-1'-carboxylic acid phenylmethyl ester (17).[16] Copper (II) triflate (13.8 mg, 38 μmol) and 2,2'-isopropylidene-bis[(4*S*)-4-*tert*-butyl-2-oxazoline] (11.2 mg, 38 μmol) were combined in a dry box under an inert atmosphere. The sealed flask was then removed from the box and connected to a nitrogen line. Anhydrous CH_2Cl_2 (3 mL) was added, whereupon a green/blue solution formed within 5 min. The solution was stirred for 3 h at room temperature. At the end of this time the solution was checked visually for the presence of undissolved copper (II) triflate. If present, stirring was continued until all the triflate salt had dissolved, forming a homogeneous green solution of the ligand complex, this was cooled to –78°C. A solution of lactam **7** (50 mg, 0.19 mmol) in CH_2Cl_2 (1 mL) was then added *via* cannula followed by the addition of freshly distilled cyclopentadiene (188 mg, 2.85 mmol). The resulting solution was warmed to room temperature and stirred for 3 h. The reaction mixture was then diluted with ethyl acetate/hexane (1:1, 10 mL), applied directly to a short column of silica gel and eluted with ethyl acetate/hexane (1:1) to remove the copper salts. Concentration *in vacuo* afforded the crude product which was purified by flash chromatography (hexane/ethyl acetate 7:1) to give the *title compound* **17** (33 mg, 53%) as a yellow oil and as a 2:1 ratio of *exo/endo* diastereomers. The enantiomeric excess was determined to be 58% by chiral HPLC by comparison with a racemic sample[a] using a Chiralpak AD column [hexane:^{i}-PrOH = 95:5, 0.3 mL min $^{-1}$, 254 nm: t_r (*exo*, major enantiomer) = 23.6 min, t_r (*exo*, minor enantiomer) = 25.5 min. t_r (*endo*, major enantiomer) = 27.8 min, t_r (*endo*, minor enantiomer) = 25.0 min]. $[\alpha]_D$= +12.25 (c = 2.4, $CHCl_3$). Chemical shifts for the minor conformer due to restricted rotation about the amide bond is indicated by an asterisk(*).

Major *Exo* isomer: ν_{max} (NaCl)/cm^{-1} (CH_2Cl_2) 3054, 2986, 1764, 1707, 1332, 1162; δ_H (300 MHz; $CDCl_3$) 1.21 (1H, bd, *J* 11.7, 3A-*H*), 1.46–1.74 (8H, m, 7-, 4'-, 5'- and 6'-CH_2), 2.23 (1H, dd, J_{gem} 11.7 and $J_{3,4}$ 4.0, 3B-*H*), 2.84 (1H, bs, 4-*H*), 3.31 (1H, bs, 1-*H*), 3.56–3.66 (1H, m, 7'A-*H*), 3.94–4.03 (1H, m, 7'B-*H*), 5.24 (2H, s, 1''-CH_2), 6.08 (1H, dd, $J_{6,5}$ 5.5 and $J_{6,4}$ 3.1, 6-*H*), 6.26 (1H, dd, $J_{5,6}$ 5.5 and $J_{5,1}$ 2.9, 5-*H*), 7.29–7.38 (5H, m, 2'''- to 6'''-C*H*); δ_C (75 MHz; $CDCl_3$) 26.1 (*C*H_2, C-6'), 27.1 (*C*H_2, C-5'), 28.6* (*C*H_2, C-6'), 29.1* (*C*H_2, C-5'), 35.1 (*C*H_2, C-4'), 37.6 (*C*H_2, C-3), 42.7 (*C*H_2, C-4), 44.6 (*C*H_2, C-7'), 49.1 (*C*H_2, C-7), 50.4 (*C*H_2, C-1), 57.1 (quat, C-2,3'), 68.2 (*C*H_2, C-1''), 68.5* (*C*H_2, C-1''), 127.8 (*C*H, C-2''' and C-6'''), 127.9* (*C*H, C-2''' and C-6'''), 128.0 (*C*H, C-4'''), 128.2* (*C*H, C-4'''), 128.5 (*C*H, C-3''' and C-5'''), 128.5* (*C*H, C-3''' and C-5'''), 133.9 (*C*H, C-6), 139.6 (*C*H, C-5), 155.3 (quat, CO- CBz), 175.5* (quat, C-2'), 182.0 (quat, C-2'); *Endo* Isomer: δ_H (300 MHz; $CDCl_3$) 1.43–1.88 (10H, m, 3-, 7-, 4'-, 5'-, 6'-CH_2), 2.81 (1H, bs, 4-*H*), 3.04 (1H, bs, 1-*H*), 3.43–3.53 (1H, m, 7'A-*H*), 4.03–4.13 (1H, m, 7'B-*H*), 5.21 (2H, s, 1''-CH_2), 6.08 (1H, dd, $J_{6,5}$ 5.8 and $J_{6,4}$ 2.9, 6-*H*), 6.13 (1H, dd, $J_{5,6}$ 5.8 and $J_{5,1}$ 2.9, 5-*H*), 7.26–7.39 (5H, m, 2'''- to 6'''-C*H*); *m/z* (EI): 325 (M^+, 1.4%) and 91 (100); HRMS (EI): Found M^+, 325.16744 $C_{20}H_{23}NO_3$, requires M^+, 325.16779.

Benzyl (6*S*)-2,3-Dimethyl-7-oxo-8-azaspiro[5.6]dodec-2-ene-8-carboxylate (18). Procedure using Cu(OTf)$_2$. Copper (II) triflate (9.7 mg, 27 μmol) and 2,2'-isopropylidene-bis[(4*S*)-4-*tert*-

[a] The racemic sample was prepared in the same fashion as above but without the addition of the chiral ligand.

butyl-2-oxazoline] (7.9 mg, 27 μmol) were combined in a dry box under an inert atmosphere. The sealed flask was then removed from the box and connected to a nitrogen line. Anhydrous CH_2Cl_2 (3 mL) was added, whereupon a green/blue solution formed within 5 min. The solution was stirred for 3 h at ambient temperature. At the end of this time the solution was checked visually for the presence of undissolved copper (II) triflate. If present, stirring was continued until all the triflate salt had dissolved, forming a homogeneous green solution of the ligand complex, which was cooled to –78 °C. A solution of lactam **7** (37 mg, 0.135 mmol) in CH_2Cl_2 (1 mL) was then added *via* cannula followed by freshly distilled 2,3-dimethyl-1,3-butadiene (166 mg, 2.02 mmol). The resulting solution was warmed to room temperature and stirred for 3 h. The reaction mixture was then diluted with ethyl acetate/hexane (1:1, 10 mL), applied directly to a short column of silica gel and eluted with ethyl acetate/hexane (1:1) to remove the copper salts. Concentration *in vacuo* afforded the crude product which was purified by flash chromatography (hexane/ethyl acetate 8:1) to give the *title compound* **18** (12 mg, 26 %) as a pale yellow oil. The enantiomeric excess was determined to be 58% by chiral HPLC by comparison with a racemic sample[a] using a Chiralpak AD column [hexane:^{i}-PrOH = 99:1, 0.3 mL min $^{-1}$, 254 nm: t_r (major enantiomer) = 41.1 min, t_r (minor enantiomer) = 39.4 min]. $[\alpha]_D$= +3.0 (c = 0.5, $CHCl_3$).

Procedure using $Cu(SbF_6)_2$. Copper (II) chloride (6.18 mg, 46 μmol) and 2,2'-isopropylidene-bis[(4*S*)-4-*tert*-butyl-2-oxazoline] (14.9 mg, 51 μmol) and $AgSbF_6$ (32 mg, 92 μmol) were combined in a dry box under an inert atmosphere. The sealed flask was then removed from the box and connected to a nitrogen line. Anhydrous CH_2Cl_2 (2 mL) was added and the flask was wrapped in aluminium foil to protect the reaction mixture from light. The heterogeneous mixture was stirred vigorously for 6 h at ambient temperature. At the end of this time the mixture was filtered through a short column of Celite and rinsed with CH_2Cl_2 (1 mL) to give a clear, dark blue solution of [Cu((*S*,*S*)-*tert*-Bu-box)]$(SbF_6)_2$ that was cooled to –78 °C. A solution of lactam **7** (60 mg, 0.23 mmol) in CH_2Cl_2 (1 mL) was then added *via* cannula followed by freshly distilled 2,3-dimethyl-1,3-butadiene (285 mg, 3.47 mmol). The resulting solution was warmed to room temperature and stirred for 24 h. The reaction mixture was diluted with ethyl acetate/hexane (1:1, 10 mL), applied directly to a short column of silica gel and eluted with ethyl acetate/hexane (1:1) to remove the copper salts. Concentration *in vacuo* afforded the crude product which was purified by flash chromatography (hexane/ethyl acetate 8:1) to give the *title compound* **18** (23 mg, 30 %) as a yellow oil. The enantiomeric excess was determined to be 94% by chiral HPLC by comparison with a racemic sample[a] using a Chiralpak AD column [hexane:^{i}-PrOH = 95:5, 0.3 mL min $^{-1}$, 254 nm: t_r (major enantiomer) = 67.7 min, t_r (minor enantiomer) = 64.3 min]. $[\alpha]_D$= +12.85 (c = 2, $CHCl_3$).

ν_{max} (NaCl)/cm^{-1} (CH_2Cl_2) 3054, 2986, 2930, 1752, 1702, 1380; δ_H (400 MHz; $CDCl_3$) 1.51 (3H, s, 3-CH_3), 1.58 (3H, s, 2-CH_3), 1.61–1.63 (1H, m, 12-CH_2), 1.68–1.71 (6H, m, 11-, 4- and 5-CH_2), 1.85 (1H, bd, *J* 16.8, 1A-*H*), 1.91–2.02 (3H, m, 10-CH_2), 2.53 (1H, bd, *J* 16.8, 1B-*H*), 3.63–3.70 (1H, m, 9A-*H*), 3.73–3.81 (1H, m, 9B-*H*), 5.19 (2H, s, 1'-CH_2), 7.27–7.35 (5H, m, 2"- to 6"-C*H*); δ_C (100 MHz; $CDCl_3$) 18.5 (*C*H$_3$, 3-CH$_3$), 19.3 (*C*H$_3$, 2-CH$_3$), 23.4 (*C*H$_2$, C-11), 26.5

(CH_2, C-4), 28.6 (CH_2, C-10), 30.5 (CH_2, C-5), 32.7 (CH_2, C-12), 40.3 (CH_2, C-1), 45.1 (CH_2, C-9), 48.5 (quat, C-6), 67.8 (CH_2, C-1'), 123.1 (quat, C-2), 124.4 (quat, C-3), 127.6 (*C*H, C-2" and C-6"), 128.0 (*C*H, C-4"), 128.5 (*C*H, C-3" and C-5"), 136.1 (quat, C-1"), 154.9 (quat, CO- CBz), 183.1 (quat, C-7); *m/z* (EI): 341 (M^+, 3.8%), 313 (M – C_2H_4, 28), 250 (M – C_7H_7, 91), 206 (135), and 91 (100); HRMS (EI): Found M^+, 341.19923 $C_{21}H_{27}NO_3$, requires M^+, 341.19909.

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