Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 437–445

TETRAHEDRON: *ASYMMETRY*

Efficient synthesis of (*S*)-3,4-dihydro-2-pivaloyloxymethyl-2*H*-pyrrole 1-oxide

Félix Busqué,[a] Pedro de March,[a,*] Marta Figueredo,[a] Josep Font,[a,*] Timothy Gallagher[b] and Sergio Milán[a]

[a]*Departament de Química, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain*
[b]*School of Chemistry, University of Bristol, Bristol BS8 1TS, UK*

Received 18 February 2002; accepted 1 March 2002

Abstract—A convenient synthesis of the title nitrone is reported. The sequence starts from ethyl L-pyroglutamate as the source of chirality and the key step is the generation of an unstable α-methoxy-*N*-carboxylate ion, which readily decomposes to an imine. The oxidation of the imine with methyl(trifluoromethyl)dioxirane provides the enantiopure nitrone, which is trapped with dimethyl acetylenedicarboxylate.

1. Introduction

Nitrones are among the most synthetically useful 1,3-dipolar species, because their cycloaddition reactions with alkenes or alkynes yield isoxazolidines or isoxazolines, respectively, which are suitable intermediates for the synthesis of bioactive compounds, mainly alkaloids.[1] Stereoselective synthesis is a major goal in organic chemistry and many efforts have been devoted to the preparation of enantiopure cycloadducts derived from 1,3-dipoles. Nevertheless, progress in the development of asymmetric versions of the 1,3-dipolar cycloaddition reaction lags far behind the advances reached in the closely related Diels–Alder process. Particularly noticeable is the relatively small number of successful 1,3-dipolar cycloadditions compared to those of Diels–Alder reactions performed in the presence of enantiopure catalysts.[2] Thus, most syntheses of enantiopure isoxazolidines achieved through a 1,3-dipolar cycloaddition process start from either a chiral non-racemic dipolarophile or nitrone.[2] During the last years, our research group has been active in this field and we have focused on all three possible approaches to the issue: use of enantiopure catalysts,[3] homochiral dipolarophiles[4] and homochiral nitrones.[5]

In relation to an ongoing program on alkaloid synthesis, we wanted to develop a convenient access to an enantiopure 2-substituted 3,4-dihydro-2*H*-pyrrole 1-oxide **1** (Fig. 1). Preparations of a few chiral nitrones with this structure are described in the literature, namely **2** (R = Me),[6] **3**,[7] **4**[8] and **5**.[9] However, all are prepared in racemic form and through methodologies which cannot be modified easily to provide enantioselective routes, since they all start from achiral materials.

Obviously, a prolinate or proline itself are appealing and inexpensive starting materials for the synthesis of a nitrone of general structure **1**, but direct oxidation of

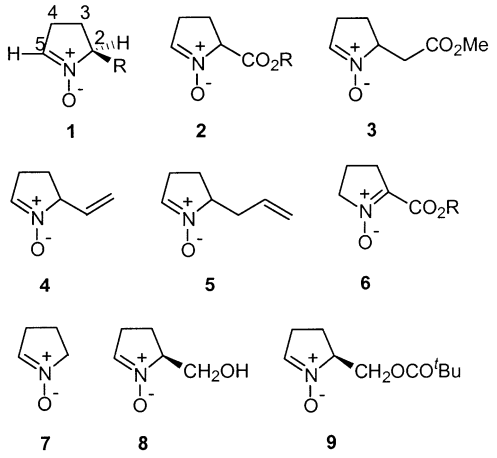


Figure 1.

* Corresponding authors. Tel.: 34-935811258; fax: 34-935811265 (P.de M.); tel.: 34-935811255; fax: 34-935811265 (J.F.); e-mail: pere.demarch@uab.es; josep.font@uab.es

0957-4166/02/$ - see front matter
PII: S0957-4166(02)00110-6

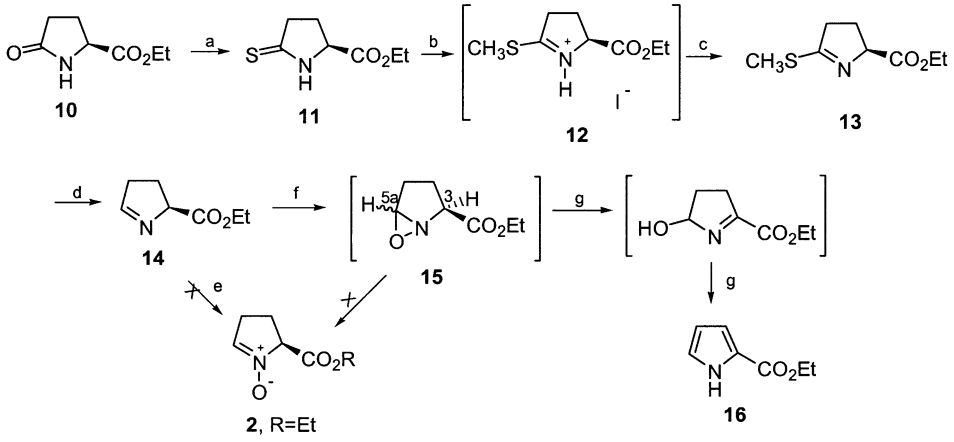
proline or its esters with several reagents affords either the conjugated or the unsubstituted achiral nitrones **6** or **7**.[10] We have reported the synthesis of the hydroxymethyl substituted nitrone **8**,[5b] formed via direct oxidation of prolinol, and a preliminary note describing the preparation of the pivaloyloxymethyl derivative **9**.[5a] Herein, we give full details for the preparation of **9**, including a new and improved synthesis of this nitrone. To the best of our knowledge there are no other reports of enantiomerically pure C(5)-monosubstituted aldonitrones. Homochiral, 5-substituted ketonitrones have been described by Oppolzer's group,[11] and the remaining enantiopure five-membered cyclic nitrones reported in the literature contain additional oxygen functionalities at C(3) and/or C(4).[12]

2. Results and discussion

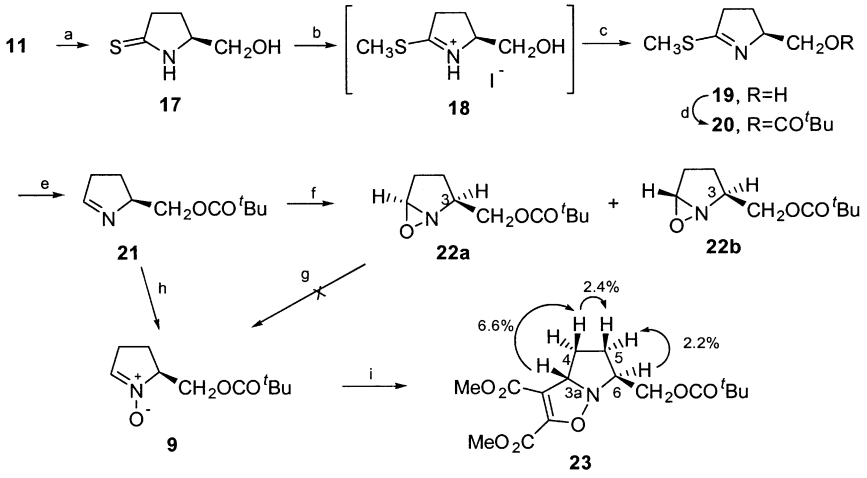
Considering these literature precedents, our first attempts were directed towards the development of an enantioselective synthesis of **2** (R = Et) starting from (+)-ethyl L-pyroglutamate, **10** (Scheme 1), which can either be purchased or easily prepared.[13] Thiolactam (+)-**11** was prepared in 90% yield by reaction of **10** with Lawesson's reagent,[14] although racemic[15] and enantiopure **11**[16] had already been prepared by other methodologies. Reaction of **11** with iodomethane gave the hydroiodide **12**, which upon treatment with aqueous $NaHCO_3$[17] afforded the imidothiolate **13** as a colourless oil in 84% overall yield. Evidence of the imidothiolate moiety are the absorptions of the methyl group at δ 2.50 and that of the imine carbon atom at δ 176.9 in the ^1H and ^{13}C NMR spectra, respectively. Since we found a unique precedent[18] regarding the desulfurisation of a non-aromatic imidothiolate to an imine we tested several reducing agents for the conversion of **13** into **14**. Attempts to achieve this transformation with Al–Hg,[18] $HSnBu_3$,[19] or $Ni(BH_4)_2$,[20] were unsuccessful, but the use of commercial W-2 Raney-Ni[21] furnished the dihydropyrrole **14** in 40% isolated yield. In its ^1H NMR spectrum, this new compound showed an absorption at δ 7.70 corresponding to the imine proton.[22,23] The moderate yield of the reduction is probably due to the low stability of **14**.

According to the literature precedents, the oxidation of an imine to a nitrone can be carried out either directly using permanganate ion,[24] dioxiranes,[25] oxaziridinium tetrafluoroborates,[26] or peracids,[25a] or through a two-step procedure involving the generation[25a,27] and rearrangement of an oxaziridine under various reaction conditions.[27a–d,27g,28] Oxidation of the aldimine **14** with permanganate ion under heterogeneous conditions or with Oxone® did not provide the target nitrone **2** (R = Et), but treatment of **14** with *m*-CPBA led to a ca. 1:1 mixture of diastereoisomeric oxaziridines **15** as evidenced by the presence of two singlets at δ 4.55 and 4.60 in the ^1H NMR spectrum attributed to C(5a)H. When this mixture was heated at 70°C, the signal at δ 4.55 had completely disappeared after 1 h, while that at δ 4.60 vanished after heating for 3 h, and the only product observed was the known pyrrole **16**,[22] formation of which is favoured by the acidity of the C(3) proton situated α to the ester group. Based on these observations we tentatively assigned the first singlet to the *cis* oxaziridine, which should decompose faster considering the stereoelectronic requirements of the process. Unfortunately, all attempts to effect the desired rearrangement of **15** to nitrone **2** under thermal activation[27b,27d] or in the presence of silica gel[27a,28c] failed and only pyrrole **16** was detected.

Since the presence of an ester moiety in the target enantiopure nitrone was not essential for our synthetic plans, we decided to focus our attention on a new target nitrone with the same carbon framework, but with a hydroxymethyl group as the substituent at position two, namely **8** or its protected variant **9**. The first step in this alternative route was the reduction of the ester functionality of thiolactam **11** with lithium borohydride (Scheme 2), the same reagent previously used



Scheme 1. (a) Lawesson's reagent, THF, rt, 1 h, 90%; (b) ICH_3, acetone, rt, 18 h, 87%; (c) $NaHCO_3$, H_2O, 97%; (d) W-2 Raney-Ni, acetone, ref., 1 h, 40%; (e) $KMnO_4$, CH_2Cl_2/H_2O or Oxone®, acetone; (f) *m*-CPBA, $CDCl_3$, 0°C, 30 min; (g) 70°C, $CDCl_3$.



Scheme 2. (a) $LiBH_4$, THF, rt, 18 h, 90%; (b) ICH_3, acetone, rt, 18 h, 92%; (c) $NaHCO_3$, H_2O, 83%; (d) ^{t}BuCOCl, DMAP, py, CH_2Cl_2, rt, 1 day, 92%; (e) W-2 Raney-Ni, acetone, ref., 1 h, 34%; (f) *m*-CPBA, CH_2Cl_2, 0°C, 1 h, 72%; (g) Δ, *hv* or SiO_2; (h) TFMD, CH_2Cl_2, −78°C, 1 h; (i) DMAD, CH_2Cl_2, rt, 18 h, 62% from **21**.

for the reduction of the analogous lactam.[29] The new compound **17**, isolated in 90% yield as a colourless solid, presents two double doublets at δ 3.54 and 3.76 in its ^{1}H NMR spectrum for the methylene group of the primary alcohol. Thiolactam **17** was converted into the hydroiodide **18** and this into the imidothiolate **19**, which was isolated as a colourless oil in 76% overall yield. Although a synthesis of **19** has already been described,[30] our sequence improves the reported overall yield from 32 to 62% starting from **10**. The hydroxyl group in **19** was then protected as the pivaloyl ester using the conventional methodology[31] providing the new pyrroline **20** in 92% yield. Reduction of **20** was best carried as above using W-2 Raney-Ni to give the unstable imine **21** in 34% yield. Its structural identification was based on the absorptions at δ 7.60 in its ^{1}H NMR spectrum due to the imine proton and the signal at δ 167.8 in the ^{13}C NMR spectrum corresponding to the imine carbon atom. In this reaction some unreacted **20** was recovered which had an identical specific rotation value as the starting **20**. This observation indicates that no racemization took place during the reduction process, in spite of the strong basic medium.

With the aim of preparing the corresponding oxaziridines, the first oxidation assays of imine **21** were performed using *m*-CPBA.[25a,27a–d,27g] These reactions yielded ca. 1:3 mixtures of diastereoisomeric compounds **22a** and **22b**, respectively. The stereochemical assignment is only tentative, based on the assumption that the oxidation takes place preferentially on the less hindered face of **21** and also on the following NMR data: proton C(3)H in **22b** is shifted upfield (δ 3.37) compared to isomer **22a** (δ 3.76), while the opposite occurs for the methylenic protons of the substituent at C(3) (δ 4.22 for **22b** and δ 4.08 and 4.16 for **22a**). These observations are in agreement with a higher steric congestion for C(3)H in **22b** and for the methylene unit in **22a**. Unfortunately, all efforts to isomerise **22** to **9** under thermal[27b,27d] or photochemical[28a,b] conditions or by treatment with silica gel[27a,28c] were unsuccessful. Additionally, oxidation of the imine **21** with dimethyldioxirane at a range of temperatures between −78 and −20°C did not afford the desired nitrone **9**.[25] Either no reaction took place or decomposition products were mainly detected. Nevertheless, the oxidation of **21** could be satisfactorily accomplished using methyl(trifluoromethyl)dioxirane.[32] Monitoring the reaction by ^{1}H NMR analysis of the reaction mixture showed the progressive decrease of the imine signal at δ 7.60, while a new absorption at δ 6.97 simultaneously increased accordingly to the formation of nitrone **9**. Addition of dimethyl acetylenedicarboxylate to the crude nitrone solution at room temperature afforded a single cycloadduct **23** in 62% overall yield from imine **21**. The assignment of the stereochemistry of **23** stands on the following significant NOE experiments: (a) irradiation of C(3a)H at δ 4.85 caused an enhancement of the signal of C(4)Hβ at δ 2.30; (b) presaturation of this last proton resulted in an increase of the signal corresponding to C(5)Hβ at δ 1.54; (c) irradiation of C(6)H at δ 3.56 produced an enhancement of C(5)Hα at δ 1.92, but not of C(5)Hβ; and (d) irradiation of C(5)Hβ increases only the signals corresponding to C(4)Hβ and C(5)Hα. The enantiomeric purity of **23** ($[\alpha]_D^{25} = -167.5$ (*c* 7.5, $CHCl_3$)) was established as $\geq$95% by ^{1}H NMR analysis using europium(III) tris[3-(trifluoromethylhydroxymethylene)-(−)-camphorate] as chiral shift reagent and employing racemic **23**, prepared from racemic **10**, as a standard. Racemic **23** showed two sets of signals for the methylenoxy group at C(6), each methoxy group and the *tert*-butyl unit. For cycloadduct (−)-**23**, prepared from enantiomerically pure lactam (*S*)-**10**, only one set of signals was observed in the presence of $Eu(tfc)_3$.

The results so far obtained completed the synthetic sequence from (+)-ethyl pyroglutamate **10** to the target

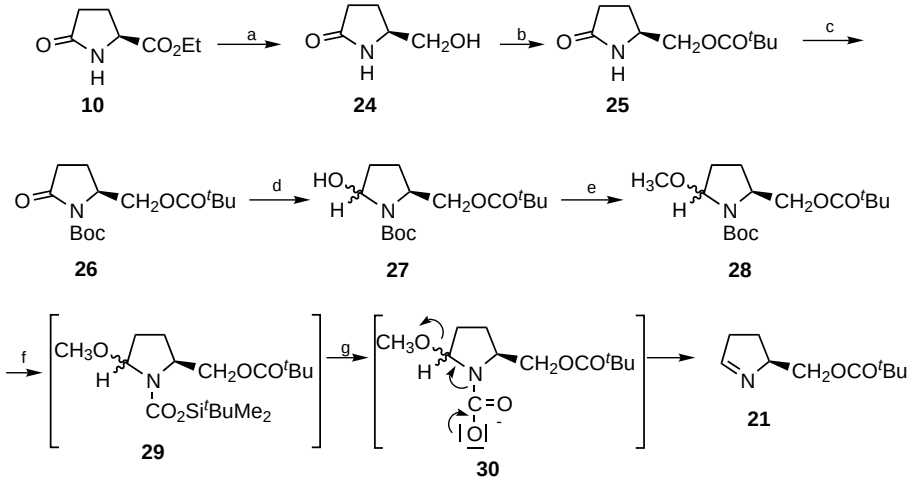
nitrone **9** with an overall yield of ca. 12%. Undoubtedly, the main drawback of the synthesis was the desulfurisation step, the yield of which we were unable to improve despite the many efforts dedicated to this end. Therefore, we decided to develop an alternative synthesis of imine **21**, according to the pathway depicted in Scheme 3. Ethyl pyroglutamate, **10**, was reduced to alcohol **24**,[33] available also commercially, in 90% yield. Protection of the primary alcohol as the pivaloate ester was achieved in 83% yield. The presence of a singlet at δ 1.15 in the ^{1}H NMR spectrum of **25** and two absorptions at δ 178.4 and 178.6 in its ^{13}C NMR spectrum revealed the formation of the desired ester. Prior to the reduction of the lactam group, the nitrogen atom was protected as the *tert*-butyl carbamate using standard methodology.[34] The new compound **26**, isolated as a solid in 88% yield, shows two singlets at δ 1.07 and 1.41 in the proton NMR spectrum and a signal at δ 149.1 in the ^{13}C NMR spectrum, in agreement with the presence of a carbamate moiety. Carefully controlled reduction of **26** with DIBAL-H[35] at −78°C for 4 h followed by treatment of the crude product with saturated aqueous ammonium chloride provided a mixture of diastereoisomeric aminals **27** in 87% yield. The NMR spectra of this mixture are complicated by the slow equilibrium between rotamers of the carbamate function at room temperature in the $CDCl_3$ solution, but a broad signal at δ 5.46 in the proton NMR spectrum is clearly diagnostic for an aminal proton. The crude material was treated with anhydrous methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid[35] to afford a mixture of the methoxy derivatives **28** in 88% yield. Their purification by column chromatography allowed the isolation of pure samples of each isomer. In the proton NMR spectrum, the less polar isomer shows a unique set of signals with a broad absorption at δ 5.18 and a singlet at δ 3.27 characteristic of the aminal proton and the methoxy group, respectively, while the second eluting isomer presents a ca. 1:1 mixture of two carbamate rotamers, evidenced by two broad signals at δ 4.90 and 5.10 and two singlets at δ 3.30 and 3.35. The mixture of diastereoisomers **28** was treated with *tert*-butyldimethylsilyl trifluoromethanesulfonate[36] to give the corresponding silyl carbamates **29** as an oily material. The analysis of the ^{1}H NMR spectrum of **29** reveals the presence of two rotamers for each stereoisomer: four doublets in the region δ 4.80–5.20 and four singlets between δ 3.20 and 3.60 are observed. We envisaged the *N*-trialkylsilyloxycarbonyl group of **29** as a masked form of an *N*-carboxylate ion **30**,[36] that should be an extremely unstable species, accessible by cleavage of the silyl carbamate with fluoride ion. Consequently, we decided to treat the mixture of isomers **29** with tetrabutylammonium fluoride in the hope that the carboxylate **30** would spontaneously decarboxylate to form the imine **21**. We were certainly pleased to isolate enantiopure **21** in 72% overall yield from the methoxy aminal **28**. To the best of our knowledge, this is the first example of synthesis of an imine from a *N*-Boc protected amide.

The overall yield for the conversion of **26** into **21** is 55%, completing an efficient synthesis of enantiopure imine **21**, which is formed in 40% yield starting from commercially available **24**.

During these synthetic studies, a series of new enantiopure 3,4-dihydro-2*H*-pyrrole derivatives have been prepared. In particular, for the target nitrone a new synthesis has been developed, markedly improving upon the preliminary sequence.

3. Experimental

Reaction mixtures were stirred magnetically. The organic extracts were dried over anhydrous sodium sulfate. Reaction solutions were concentrated using a rotary evaporator at 5–10 Torr. Flash chromatography was performed using Merck silica gel (230–400 mesh). Infrared spectra were recorded on a Nicolet 5 ZDX



Scheme 3. (a) $LiBH_4$, THF, rt, 48 h, 90%; (b) ^{t}BuCOCl, DMAP, py, CH_2Cl_2, rt, 1 day, 83%; (c) $(Boc)_2O$, Et_3N, CH_2Cl_2, rt, 1 day, 88%; (d) DIBAL, THF, −78°C, 4 h, 87%; (e) *p*-TsOH, MeOH, rt, 30 min, 88%; (f) $CF_3SO_3Si^tBuMe_2$, 2,6-lutidine, CH_2Cl_2, rt, 10 min; (g) nBu$_4$NF, THF, rt, 1 h, 72% from **28**.

spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-250-WB or AM-400-WB instruments at 250 or 400 MHz and 62.5 or 100 MHz, respectively, in $CDCl_3$ solutions. Only those spectra recorded in the Bruker AM-400-WB are specified. Mass spectra were performed on a Hewlett–Packard 5985B instrument at 70 eV; only peaks with higher intensity than 20% are reported, unless they belong to molecular ions or to significant fragments.

3.1. Ethyl (*S*)-4,5-dihydro-2(3*H*)-thioxopyrrole-5-carboxylate 11

A solution of ethyl L-pyroglutamate[13] (2.00 g, 12.7 mmol) in anhydrous THF (30 mL) under nitrogen atmosphere was treated with Lawesson's reagent (2.56 g, 6.33 mmol). The reaction mixture was kept at rt for 1 h. Flash chromatography of the crude material (4.60 g) using hexane/ethyl acetate (3:2) as eluent afforded **11**[16] as a solid (1.98 g, 11.4 mmol, 90%); mp 35–36°C (lit.[16a] mp 43–45°C; lit.[16b] yellow oil). $[\alpha]_D^{20}=+12.5$ (*c* 4.0, ethanol).

3.2. Ethyl (*S*)-3,4-dihydro-5-methylthio-2*H*-pyrrole-2-carboxylate 13

To a solution of **11** (1.97 g, 11.4 mmol) in acetone (40 mL), iodomethane (0.70 mL, 11.3 mmol) was added slowly and the mixture was stirred at rt overnight. A colourless precipitate was formed. Ether (30 mL) was added and the solid was filtered and washed with ether (2×10 mL) yielding the hydroiodide **12** (3.11 g, 9.9 mmol, 87%), which was dissolved in CH_2Cl_2 (30 mL). This solution was washed with saturated aqueous $NaHCO_3$ (2×60 mL) and removal of the organic solvent yielded compound **13** as a colourless oil (1.80 g, 9.6 mmol, 84% from **11**). An analytical sample was obtained by distillation; bp 92–93°C/2 Torr; IR (film) 2982, 2932, 1738, 1585, 1188 cm^{-1}; ^{1}H NMR δ 1.28 (t, $J=5.7$ Hz, 3H, CH_3), 2.18 (m, 1H, H-3), 2.23 (m, 1H, H-3), 2.50 (s, 3H, SCH_3), 2.74 (m, 2H, H-4), 4.21 (q, $J=5.7$ Hz, 2H, OCH_2), 4.70 (dd, $J=5.2$ Hz, $J'=4.8$ Hz, 1H, H-2); ^{13}C NMR δ 13.7/14.1 (CH_3/SCH_3), 27.6 (C-3), 38.6 (C-4), 60.9 (OCH_2), 73.5 (C-2), 172.7 (CO), 176.9 (C-5); MS (*m*/*z*): 187 (M$^+$, 19), 114 (100), 100 (33). Anal. calcd for $C_8H_{13}NO_2S$: C, 51.31; H, 7.00; N, 7.48; S, 17.12. Found: C, 51.29; H, 6.99; N, 7.47; S, 17.02%. $[\alpha]_D^{20}=+80.6$ (*c* 6.0, $CHCl_3$).

3.3. Ethyl (*S*)-3,4-dihydro-2*H*-pyrrole-2-carboxylate 14

A mixture of **13** (550 mg, 2.9 mmol) and commercial W-2 Raney-Ni (5.5 g) in acetone (40 mL) was heated at reflux for 1 h. The solution was filtered through Celite® and the solid was extracted with boiling ethyl acetate (30 mL) for 15 min. The combined filtrates were concentrated to afford an oil (290 mg), which was purified by flash chromatography using ethyl acetate as eluent furnishing the following fractions: starting **13** (30 mg) and imine **14** as an unstable colourless oil (165 mg, 1.17 mmol, 40%); ^{1}H NMR δ 1.20 (t, $J=6.2$ Hz, 3H, CH_3), 2.05 (m, 2H, H-3), 2.60 (m, 2H, H-4), 4.18 (q, $J=6.2$ Hz, 2H, OCH_2), 4.67 (m, 1H, H-2), 7.70 (s, 1H, H-5). $[\alpha]_D^{20}=+14.1$ (*c* 8.5, $CHCl_3$).

3.4. Ethyl (3*S*,5a*R*)- and (3*S*,5a*S*)-tetrahydropyrrolo[1,2-*b*]oxaziridine-3-carboxylate 15

A solution of imine **14** (20 mg, 0.14 mmol) in $CDCl_3$ (0.6 mL) at 0°C was treated with *m*-CPBA (95% purity, 25 mg, 0.14 mmol). After 30 min the ^{1}H NMR analysis of the mixture showed the presence of a ca. 1:1 mixture of *cis*- and *trans*-**15**; *cis*-**15**: ^{1}H NMR δ 1.26 (t, $J=6.5$ Hz, 3H, CH_3), 1.80 (m, 2H), 2.05 (m, 1H), 2.40 (m, 1H), 3.80 (dd, $J=10.4$ Hz, $J'=1.6$ Hz, 1H, H-3), 4.25 (q, $J=6.5$ Hz, 2H, OCH_2), 4.55 (s, 1H, H-5a); *trans*-**15**: ^{1}H NMR δ 1.22 (t, $J=6.5$ Hz, 3H, CH_3), 1.80 (m, 2H), 2.05 (m, 1H), 2.40 (m, 1H), 4.05–4.20 (m, 1H, H-3 and q, $J=6.5$ Hz, 2H, OCH_2), 4.60 (s, 1H, H-5a).

On heating this sample at 70°C the signals of *cis*-**15** disappeared after 1 h, and the absorptions of *trans*-**15** disappeared after 3 h. The only observable new signals corresponded to pyrrole **16**;[22] ^{1}H NMR δ 1.30 (t, $J=6.5$ Hz, 3H, CH_3), 4.28 (q, $J=6.5$ Hz, 2H, OCH_2), 6.20 (dd, $J=6.4$ Hz, $J'=2.8$ Hz, 1H, H-4), 6.84 (m, 1H, H-3), 6.91 (m, 1H, H-5).

3.5. (*S*)-4,5-Dihydro-5-hydroxymethylpyrrole-2(3*H*)-thione 17

To a solution of thiolactam **11** (1.70 g, 9.83 mmol) in THF (20 mL) at 0°C, a solution of $LiBH_4$ in THF (2.0 M, 5.4 mL, 10.7 mmol) was slowly added. The mixture was kept at rt overnight, then cooled at 0°C and neutralised with 20% aqueous acetic acid (8 mL). The organic solvent was removed under vacuum, the formed precipitate was filtered off and the aqueous solution was introduced in a Dowex 50WX8-400 column previously washed with HCl 2M (150 mL) and water (150 mL). Elution with water afforded a colourless solid (2.01 g), which was washed with hot acetone (50 mL). The acetone solution was concentrated to yield a solid (1.56 g). Purification by flash chromatography using chloroform/methanol (18:1) as eluent afforded **17** as a colourless solid (1.17 g, 8.96 mmol, 90%); mp 124–125°C; IR (KBr) 3217, 2972, 2928, 2876, 1536, 1289 cm^{-1}; ^{1}H NMR δ 1.84 (m, 1H, H-4), 2.26 (m, 1H, H-4), 2.91 (m, 2H, H-3), 3.54 (dd, $J=11.0$ Hz, $J'=8.0$ Hz, 1H, CH_2O), 3.76 (dd, $J=11.0$ Hz, $J'=3.5$ Hz, 1H, CH_2O), 4.06 (m, 1H, H-5), 8.60 (br s, 1H, NH); ^{13}C NMR δ 25.9 (C-4), 44.3 (C-3), 64.7/65.5 (C-5/CH_2O), 206.9 (C-2); MS (*m*/*z*): 131 (M$^+$, 91), 100 (100), 67 (45). Anal. calcd for C_5H_9NOS: C, 45.78; H, 6.91; N, 10.68; S, 24.44. Found: C, 45.80; H, 6.86; N, 10.58; S, 24.35%. $[\alpha]_D^{20}=+13.4$ (*c* 1.9, acetone).

3.6. (*S*)-3,4-Dihydro-2-hydroxymethyl-5-methylthio-2*H*-pyrrole 19

To a solution of **17** (1.01 g, 7.71 mmol) in acetone (25 mL), iodomethane (0.70 mL, 11.3 mmol) was added slowly and the mixture was stirred at rt overnight. A colourless precipitate was formed. Ether (20 mL) was added and the solid was filtered and washed with ether (2×10 mL) yielding the hydroiodide **18** (1.93 g, 7.07 mmol, 92%), that was dissolved in ethyl acetate (30 mL). This solution was washed with saturated aqueous

$NaHCO_3$ (2×20 mL) and removal of the organic solvent yielded compound **19**[30] as a colourless oil (855 mg, 5.90 mmol, 76% from **17**); IR (KBr) 3364, 2928, 2874, 1587, 1100 cm^{-1}; ^1H NMR δ 1.72 (m, 1H, H-3), 2.09 (m, 1H, H-3), 2.15 (br s, 1H, OH), 2.40 (s, 3H, SCH_3), 2.65 (m, 2H, H-4), 3.49 (dd, $J=11.0$ Hz, $J'=7.5$ Hz, 1H, CH_2O), 3.83 (dd, $J=11.0$ Hz, $J'=2.7$ Hz, 1H, CH_2O), 4.15 (m, 1H, H-2); ^{13}C NMR δ 13.6 (SCH_3), 27.4 (C-3), 38.6 (C-4), 66.6 (CH_2O), 70.8 (C-2), 174.1 (C-5); MS (m/z): 145 (M^+, 18), 114 (100), 61 (35). $[\alpha]_D^{20}=+97.2$ (c 5.3, $CHCl_3$); lit.[30] $[\alpha]_D^{20}=+78.1$ (c 2.2, $CHCl_3$).

3.7. (*S*)-3,4-Dihydro-5-methylthio-2-pivaloyloxymethyl-2*H*-pyrrole 20

To a solution of **19** (400 mg, 2.76 mmol), DMAP (130 mg, 1.0 mmol) and pyridine (0.45 mL, 5.60 mmol) in CH_2Cl_2 (25 mL) at 0°C, pivaloyl chloride (0.69 mL, 5.60 mmol) was added slowly and the mixture was stirred at rt for 1 day. The solvent was removed, the solid (1.80 g) was dissolved in $CHCl_3$ (20 mL) and the solution was washed with saturated aqueous $NaHCO_3$ (2×20 mL). Flash chromatography of the crude material (800 mg) using hexane/ethyl acetate (4:1) as eluent afforded **20** as a colourless oil (580 mg, 2.53 mmol, 92%); IR (KBr) 2970, 2874, 1734, 1591, 1285, 1157 cm^{-1}; ^1H NMR δ 1.10 (s, 9H, ^{t}Bu), 1.76 (m, 1H, H-3), 2.10 (m, 1H, H-3), 2.38 (s, 3H, SCH_3), 2.60 (m, 2H, H-4), 4.13 (d, $J=5.1$ Hz, 2H, CH_2O), 4.27 (m, 1H, H-2); ^{13}C NMR δ 13.6 (SCH_3), 26.4 (C-3), 27.4 ($C(CH_3)_3$), 38.6/38.7 (C-4/$C(CH_3)_3$), 66.6 (CH_2O), 70.8 (C-2), 174.3 (C-5), 178.3 (CO); MS (m/z): 230 (M^++1, 20), 127 (73), 114 (100), 80 (51), 61 (25), 57 (88), 55 (20), 41 (57). Anal. calcd for $C_{11}H_{19}NO_2S$: C, 57.61; H, 8.35; N, 6.11; S, 13.98. Found: C, 57.72; H, 8.39; N, 5.82; S, 13.73%. $[\alpha]_D^{20}=+22.6$ (c 10.6, $CHCl_3$).

3.8. (*S*)-3,4-Dihydro-2-pivaloyloxymethyl-2*H*-pyrrole 21 from 20

A mixture of **20** (440 mg, 1.92 mmol) and commercial W-2 Raney-Ni (4.5 g) in acetone (40 mL) was heated at reflux for 1 h. The solution was filtered through Celite® and the solid was extracted with boiling ethyl acetate (30 mL) for 15 min. The combined filtrates were concentrated to afford an oil (320 mg), that was purified by flash chromatography using hexane/ethyl acetate (1:2) as eluent and furnishing the following fractions: starting **20** (55 mg) and imine **21** (106 mg, 0.58 mmol, 34% considering the recovered **20**) as an unstable colourless oil. Recovered **20**: $[\alpha]_D^{20}=+22.2$ (c 2.7, $CHCl_3$); **21**: IR (film) 2971, 2875, 1728, 1697, 1461, 1156 cm^{-1}; ^1H NMR δ 1.10 (s, 9H, ^{t}Bu), 1.53 (m, 1H, H-3), 1.93 (m, 1H, H-3), 2.55 (m, 2H, H-4), 4.17 (d, $J=5.1$ Hz, 2H, CH_2O), 4.27 (m, 1H, H-2), 7.60 (s, 1H, H-5); ^{13}C NMR δ 23.1 (C-3), 27.0 ($C(CH_3)_3$), 37.0 (C-4), 38.7 ($C(CH_3)_3$), 66.5 (CH_2O), 71.5 (C-2), 167.8 (C-5), 178.3 (CO); MS (m/z): 184 (M^++1, 41), 57 (100), 41 (55). $[\alpha]_D^{20}=+64.4$ (c 6.7, $CHCl_3$).

3.9. (3*S*,5a*S*)- and (3*S*,5a*R*)-3-Pivaloyloxymethyltetrahydropyrrolo[1,2-*b*]oxaziridine 22a and 22b

A solution of imine **21** (90 mg, 0.49 mmol) in CH_2Cl_2 (5.0 mL) at 0°C under a nitrogen atmosphere was treated with *m*-CPBA (95% purity, 89 mg, 0.50 mmol) previously dried over anhydrous $MgSO_4$. The mixture was kept at this temperature for 1 h. The solvent was removed, the residue (210 mg) was dissolved in $CHCl_3$ and the solution was washed with 10% aqueous Na_2CO_3 (2×10 mL). Removal of the solvent yielded a colourless oil identified as a 1:3 mixture of **22a** and **22b**, respectively (70 mg, 0.35 mmol, 72%); IR (film) 2972, 2875, 1730, 1284, 1157 cm^{-1}; ^{13}C NMR δ 20.8/21.5 (C-4/C-5), 27.0 and 27.3 ($C(CH_3)_3$), 38.8 ($C(CH_3)_3$), 64.2/64.7/65.5 (CH_2O/C-3), 81.1 and 81.3 (C-5a), 178.4 (CO); MS (m/z): 200 (M^++1, 1), 97 (31), 84 (100), 57 (83); **22a**: ^1H NMR (from the mixture) δ 1.18 (s, 9H, ^{t}Bu), 1.50–1.80 (m, 2H), 1.80–2.10 (m, 1H), 2.35 (dd, $J=14.6$ Hz, $J'=10.0$ Hz, 1H, H-5), 3.76 (m, 1H, H-3), 4.08 (dd, $J=11.7$ Hz, $J'=5.9$ Hz, 1H, CH_2O), 4.16 (dd, $J=11.7$ Hz, $J'=4.4$ Hz, 1H, CH_2O), 4.57 (s, 1H, H-5a); **22b**: ^1H NMR (from the mixture) δ 1.20 (s, 9H, ^{t}Bu), 1.50–1.80 (m, 2H), 1.80–2.10 (m, 1H), 2.40 (dd, $J=14.6$ Hz, $J'=8.0$ Hz, 1H, H-5), 3.37 (dq, $J=10.3$ Hz, $J'=6.6$ Hz, 1H, H-3), 4.22 (d, $J=6.6$ Hz, 2H, CH_2O), 4.57 (s, 1H, H-5a).

3.10. (*S*)-3,4-Dihydro-2-pivaloyloxymethyl-2*H*-pyrrole 1-oxide 9

A solution of imine **21** (130 mg, 0.71 mmol) in CH_2Cl_2 (10 mL) at −78°C and protected from the light was treated with a solution of TFMD in trifluoroacetone[32] (438 mM, 1.9 mL, 0.85 mmol). After 1 h the solvent was removed and the oily residue (154 mg) was identified as nitrone **9** and used immediately; ^1H NMR δ 1.18 (s, 9H, ^{t}Bu), 2.12 (m, 1H, H-3), 2.39 (m, 1H, H-3), 2.65 (m, 2H, H-4), 4.10 (m, 1H, H-2), 4.32 (dd, $J=10.7$ Hz, $J'\approx1.0$ Hz, 1H, CH_2O), 4.60 (dd, $J=10.7$ Hz, $J'\approx1.0$ Hz, 1H, CH_2O), 6.97 (s, 1H, H-5). Several other minor absorptions were also observed.

3.11. Dimethyl (3a*S*,6*S*)-3a,4,5,6-tetrahydro-6-pivaloyloxymethylpyrrolo[1,2-*b*]isoxazole-2,3-dicarboxylate 23

To a solution of nitrone **9** (154 mg) in CH_2Cl_2 (10 mL), dimethyl acetylenedicarboxylate (0.15 mL, 1.12 mmol) was added and the mixture was kept at rt overnight. Flash chromatography of the crude material (270 mg) using hexane/ethyl acetate (2:1) as eluent afforded adduct **23** (151 mg, 0.44 mmol, 62% from imine **21**); IR (film) 2961, 2912, 1754, 1727, 1656, 1286, 1137 cm^{-1}; ^1H NMR (400 MHz) δ 1.15 (s, 9H, ^{t}Bu), 1.54 (m, 1H, H-5β), 1.92 (m, 1H, H-5α), 2.04 (m, 1H, H-4α), 2.30 (m, 1H, H-4β), 3.56 (m, 1H, H-6), 3.72 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.15 (dd, $J=11.3$ Hz, $J'=5.6$ Hz, 1H, CH_2O), 4.19 (dd, $J=11.3$ Hz, $J'=5.6$ Hz, 1H, CH_2O), 4.85 (br t, $J_{3a,4\beta}\approx J_{3a,4\alpha}\approx6.1$ Hz, 1H, H-3a); ^{13}C NMR δ 27.1 ($C(CH_3)_3$), 24.7/30.4 (C-4/C-5), 38.7 ($C(CH_3)_3$), 51.8/53.1 (2×OCH_3), 64.8 (CH_2O), 69.1/69.5 (C-3a/C-6), 109.1 (C-3), 151.4 (C-2), 162.6/168.8 (2×CO_2Me), 178.2 (CO_2^tBu); MS (m/z): 341 (M^+, 2), 256

(100), 224 (29), 149 (94), 84 (24), 71 (54), 57 (55). Anal. calcd for $C_{16}H_{23}NO_7$: C, 56.30; H, 6.79; N, 4.10. Found: C, 56.11; H, 6.90; N, 3.91%. $[\alpha]_D^{20}=-167.5$ (*c* 7.5, $CHCl_3$).

3.12. (*S*)-4,5-Dihydro-5-pivaloyloxymethyl-2(3*H*)-pyrrolone 25

To a solution of **24**[33] (5.58 g, 48.5 mmol), DMAP (5.92 g, 48.5 mmol) and pyridine (5.10 mL, 63.3 mmol) in CH_2Cl_2 (280 mL) at 0°C, pivaloyl chloride (11.9 mL, 96.9 mmol) was added slowly and the mixture was stirred at rt for 1 day. The solvent was removed and the solid was extracted with ethyl acetate (20 mL). Filtration of the residual solid and removal of the solvent yielded an oil. Purification by flash chromatography using ethyl acetate as eluent afforded **25** as a colourless solid (8.01 g, 40.2 mmol, 83%); mp 64–65°C; IR (KBr) 3255, 2973, 1730, 1652, 1286, 1166 cm^{-1}; ^1H NMR δ 1.15 (s, 9H, ^{t}Bu), 1.80 (m, 1H, H-4), 2.25 (m, 3H, H-4, 2H-3), 3.85 (m, 2H, H-5, CH_2O), 4.18 (dd, $J=10.2$ Hz, $J'=2.9$ Hz, 1H, CH_2O), 6.30 (br s, 1H, NH); ^{13}C NMR δ 23.5 (C-4), 27.6 ($C(CH_3)_3$), 30.0 (C-3), 38.3 ($C(CH_3)_3$), 53.3 (C-5), 67.2 (CH_2O), 178.4/178.6 (C-2/CO); MS (*m*/*z*): 200 (M^++1, 5), 97 (32), 84 (100). Anal. calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.19; H, 8.65; N, 6.88%. $[\alpha]_D^{20}=+32.0$ (*c* 5.2, $CHCl_3$).

3.13. (*S*)-*N*-(*tert*-Butoxycarbonyl)-4,5-dihydro-5-pivaloyloxymethyl-2(3*H*)-pyrrolone 26

To a solution of **25** (2.58 g, 12.9 mmol), $(Boc)_2O$ (5.63 g, 25.8 mmol) and triethylamine (1.79 mL, 12.9 mmol) in CH_2Cl_2 (20 mL) at 0°C, another solution of DMAP (3.15 g, 25.8 mmol) in CH_2Cl_2 (10 mL) was added slowly and the mixture was stirred at rt for 1 day. Flash chromatography of the crude material using hexane/ethyl acetate (1:1) as eluent afforded **26** as a solid (3.40 g, 11.3 mmol, 88%); mp 62–63°C; ^1H NMR δ 1.07 (s, 9H, ^{t}Bu), 1.41 (s, 9H, O^{t}Bu), 1.81 (m, 1H, H-4), 2.05 (m, 1H, H-4), 2.29 (ddd, $J=17.6$ Hz, $J'=9.8$, $J''=2.5$ Hz, 1H, H-3), 2.53 (dt, $J_{3,3}=17.6$ Hz, $J_{3,4}=10.7$ Hz, $J_{3,4}=9.7$ Hz, 1H, H-3), 3.98 (m, 1H, CH_2O), 4.23 (m, 2H, H-5, CH_2O); ^{13}C NMR δ 20.6 (C-4), 26.8 ($C(CH_3)_3$), 27.7 ($OC(CH_3)_3$), 31.3 (C-3), 38.4 ($C(CH_3)_3$), 55.8 (C-5), 64.4 (CH_2O), 82.8 ($OC(CH_3)_3$), 149.1 (NCOO), 173.7/177.6 (C-2/CO). Anal. calcd for $C_{15}H_{25}NO_5$: C, 60.17; H, 8.42; N, 4.68. Found: C, 60.42; H, 8.33; N, 4.58%. $[\alpha]_D^{20}=-40.5$ (*c* 5.1, $CHCl_3$).

3.14. (2*R*,5*S*)- and (2*S*,5*S*)-*N*-(*tert*-Butoxycarbonyl)-2-hydroxy-5-pivaloyloxymethylpyrrolidine 27

To a solution of **26** (300 mg, 1.00 mmol) in dry THF (3 mL) at −78°C, a solution of DIBAL-H in THF (1.0 M, 1.1 mL, 1.10 mmol) was slowly added. The mixture was stirred at −78°C for 4 h, quenched with saturated aqueous NH_4Cl (2 mL) and allowed to warm to rt. The mixture was extracted with ethyl acetate (3×20 mL). Flash chromatography of the crude material using hexane/ethyl acetate (4:1) as eluent afforded a mixture of diastereoisomers **27** as a colourless oil (263 mg, 0.87 mmol, 87%); ^1H NMR δ 1.10 (s, 9H, ^{t}Bu), 1.37 (s, 9H, O^{t}Bu), 1.75–1.95 (m, 4H, H-3, H-4), 3.81 (br s, 1H, OH), 3.90–4.05 (m, 2H, CH_2O), 4.15 (dd, $J=10.6$ Hz, $J'=3.4$ Hz, 1H, H-5), 5.46 (m, 1H, H-2); ^{13}C NMR δ 25.8 (C-4), 27.0 ($C(CH_3)_3$), 28.2 ($OC(CH_3)_3$), 30.9 (C-3), 38.6 ($C(CH_3)_3$), 55.8 (C-5), 64.6 (CH_2O), 80.6 ($OC(CH_3)_3$), 82.5 (C-2), 154.4 (NCO), 178.0 (CO). Anal. calcd for $C_{15}H_{27}NO_5$: C, 59.78; H, 9.03; N, 4.65. Found: C, 59.64; H, 9.19; N, 4.61%.

3.15. (2*R*,5*S*)- and (2*S*,5*S*)-*N*-(*tert*-Butoxycarbonyl)-2-methoxy-5-pivaloyloxymethylpyrrolidine 28

To a solution of **27** (400 mg, 1.33 mmol) in methanol (5 mL) at 0°C, was added *p*-TsOH (10 mg) and the mixture was stirred at rt for 30 min. The solvent was removed, the oil was dissolved in CH_2Cl_2 (25 mL) and the resulting solution was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (5 mL). Removal of the organic solvent yielded compound **28** as a mixture of diastereoisomers (368 mg, 1.17 mmol, 88%). Pure samples of each isomer as colourless oils were obtained by flash chromatography using hexane/ethyl acetate (4:1) as eluent. Major and less polar isomer: ^1H NMR δ 1.17 (s, 9H, ^{t}Bu), 1.45 (s, 9H, O^{t}Bu), 1.70–2.10 (m, 4H, H-3, H-4), 3.27 (s, 3H, OCH_3), 4.00 (br m, 2H, CH_2O), 4.30 (br m, 1H, H-5), 5.18 (br d, 1H, H-2); ^{13}C NMR δ 27.1 ($C(CH_3)_3$), 28.3 ($OC(CH_3)_3$), 31.4/32.1 (C-4/C-3), 38.8 ($C(CH_3)_3$), 55.2/56.2 (OCH_3/C-5), 66.0 (CH_2O), 80.4 ($OC(CH_3)_3$), 89.4 (C-2), 178.3 (CO). Minor and more polar isomer: ^1H NMR δ 1.17 (s, 9H, ^{t}Bu), 1.43 (s, 9H, O^{t}Bu), 1.70–2.00 (m, 3H, H-3, H-4), 2.20 (m, 1H, H-3/H-4), 3.30 (s)+3.35 (s) (3H, OCH_3), 3.90–4.10 (m, 3H, CH_2O, H-5), 4.90 (br s)+5.10 (br s) (1H, H-2). Mixture of diastereoisomers: Anal. calcd for $C_{16}H_{29}NO_5$: C, 60.92; H, 9.27; N, 4.44. Found: C, 60.66; H, 9.93; N, 4.36%.

3.16. (2*R*,5*S*)- and (2*S*,5*S*)-*N*-(*tert*-Butyldimethylsilyloxycarbonyl)-2-methoxy-5-pivaloyloxymethylpyrrolidine 29

To a solution of **28** (1.57 g, 5.00 mmol) and 2,6-lutidine (2.31 mL, 19.9 mmol) in CH_2Cl_2 (25 mL) at 0°C, *tert*-butyldimethylsilyl trifluoromethanesulfonate (3.43 mL, 14.9 mmol) was added slowly and the mixture was stirred at rt for 10 min. The solvent was removed, the oil was dissolved in ethyl ether (40 mL) and the solution was washed with saturated aqueous NH_4Cl (40 mL) and brine (30 mL). Partial distillation of volatile components from the crude material afforded a residue containing a mixture of diastereoisomers **29** contaminated with silylated compounds; ^1H NMR δ 0.24 (s, 6H, $SiMe_2$), 0.91 (s, 9H, Si^{t}Bu), 1.12 (s, 9H, O^{t}Bu), 1.70–2.15 (m, 4H, H-3, H-4), 3.23 (s)+3.27 (s)+3.35 (s)+3.61 (s) (3H, OCH_3), 3.85–4.15 (m, 2H, CH_2O), 4.24 (m, 1H, H-5), 4.88 (d)+5.02 (d)+5.11 (d)+5.21 (d) (1H, H-2).

3.17. Preparation of 21 from 29

A solution of **29** (1.50 g, 4.00 mmol) in THF (15 mL) at 0°C, was treated with tetra-*n*-butylammonium

fluoride in THF (1.0 M, 4.0 mL, 4.0 mmol) and the mixture was stirred at rt for 1 h. The solvent was removed, the oil was dissolved in CH_2Cl_2 (20 mL) and the solution was washed with saturated aqueous NH_4Cl (20 mL) and brine (10 mL). Flash chromatography of the crude material using hexane/ethyl acetate (1:1) as eluent afforded **21** as a colourless oil (659 mg, 3.60 mmol, 72% from **28**). For physical and spectroscopic data of **21** see Section 3.8.

Acknowledgements

We gratefully acknowledge financial support of DGES (project PB97-0215) and CIRIT (1999SGR-00091). We also thank DGES for a grant to S.M. and CIRIT for a grant to F.B. We acknowledge Marc Comas for scaling up some of the described reactions.

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