Synthesis of (*S*)-3,4-Dihydro-2-pivaloyloxymethyl-2*H*-pyrrole 1-Oxide

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The synthesis of a series of new enantiopure 3,4-dihydro-2*H*-pyrrole derivatives including the title nitrone and its cycloaddition product to dimethyl acetylenedicarboxylate is described.

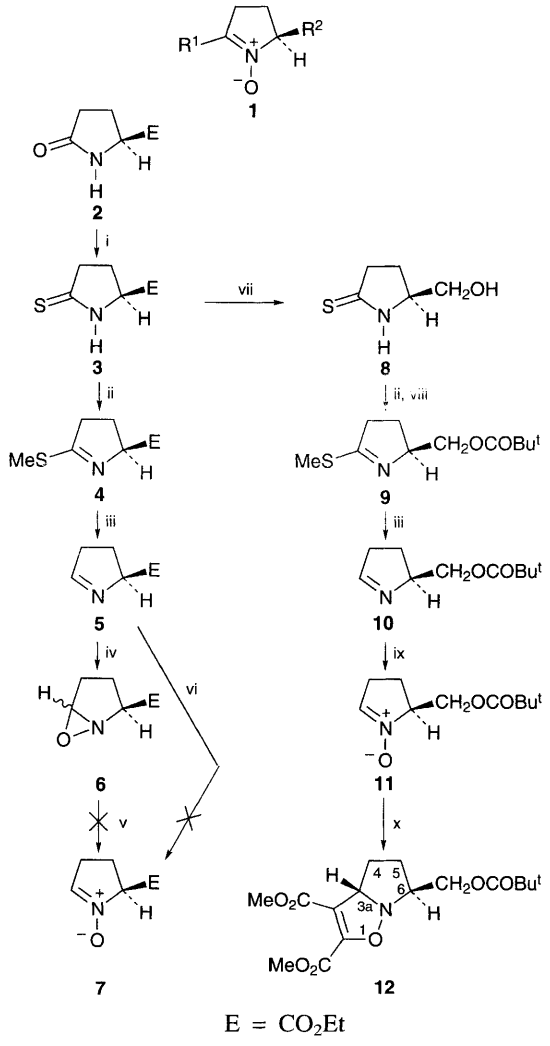
1,3-Dipolar cycloadditions have become of increasing importance in recent years for the preparation of natural products, mainly alkaloids.[1] Particularly useful are the isoxazolidine cycloadducts formed in the reaction between nitrones and alkenes, since they can be further elaborated to provide polyfunctionalized cyclic or acyclic compounds with complete control of the relative stereochemistry. Since the preparation of enantiomerically pure compounds is one of the major challenges in organic chemistry, the availability of enantiopure nitrones is most desirable.

To date, few enantiomerically pure five-membered cyclic nitrones have been described in the literature, with those known containing additional oxygen functionality at C-3 and/or C-4.[2] There are a large number of interesting alkaloids incorporating a 2,5-disubstituted pyrrolidine that should be readily available *via* 2-substituted 3,4-dihydro-2*H*-pyrrole 1-oxide **1**,[3] but to the best of our knowledge, there are no reports of enantiomerically pure monosubstituted nitrones of this type. A related case (**1**, R^1 = C_7H_{15}, R^2 = $CONR_2$) has recently been described by Oppolzer.[4]

As part of a continuing study[5] into new methods for alkaloid synthesis, we required access to nitrone **1** (R^1 = H, R^2 = CO_2R), or a synthetic equivalent, in enantiomerically pure form. Our initial target molecule was (*S*)-2-ethoxycarbonyl-3,4-dihydro-2*H*-pyrrole 1-oxide, **7**. The corresponding methyl ester has been prepared in racemic form,[6] but this route, with the low yields reported, was not attractive for our purposes.

Starting with the commercially available L-(+)-ethyl pyroglutamate **2**, an alternative approach to nitrone **7** was evaluated (Scheme 1). Thionation[7,8] of **2** gave thiolactam **3** {$[\alpha]_D^{25}$ + 12.5 (*c* 4.0, EtOH)} in 90% yield and treatment of **3** with iodomethane followed by aqueous $NaHCO_3$ provided the imidothiolate **4** {$[\alpha]_D^{25}$ + 80.6 (*c* 6.0, $CHCl_3$)} in 84% yield. Desulfuration of **4** was unsuccessful under a range of conditions [$Ni(BH_4)_2$,[9] Al–Hg,[10] or $HSnBu_3$[11]], but reduction to give the dihydropyrrole **5** {$[\alpha]_D^{25}$ + 14.1 (*c* 8.5, $CHCl_3$)} was achieved using Raney Ni[12] in moderate yield (40%). Conversion of an imine into a nitrone can be carried out either directly (using permanganate ion,[13] dioxiranes[14,15] or oxaziridium tetrafluoroborates[16]) or through a two-step sequence involving the generation[14,17–19] and rearrangement[14,17,18,20] of an oxaziridine. While MCPBA-mediated oxidation of **5** led to oxadiridine **6** (as a *ca.* 1 : 1 mixture of diastereoisomers), all attempts to effect the desired rearrangement under either thermal conditions[14,18] or in the presence of silica gel[17] failed. The only product observed was ethyl pyrrole-2-carboxylate, and this is attributed to the acidity of the proton adjacent to the ester moiety leading to a facile pathway for aromatisation. Equally, we were unable to generate nitrone **7** directly by oxidation of imine **5** with $KMnO_4$ or oxone (potassium peroxymonosulfate); complex mixtures of products were obtained.

The presence of an ester moiety in nitrone **7** was desirable, but not essential to our future plans. A 2-hydroxymethyl unit would furnish the necessary carbon framework and functionality, and should also provide a stable and more useful nitrone derivative. Reduction of thiolactam **3** gave alcohol **8** {$[\alpha]_D^{25}$ + 13.4 (*c* 1.9, acetone)} in 91% yield. Conversion of **8** to the corresponding imidothiolate, followed by protection of the primary hydroxy unit, gave pivaloate **9** {$[\alpha]_D^{25}$ + 22.6 (*c* 10.6, $CHCl_3$)} in 71% yield. Reduction of **9** was again best carried out using Raney Ni to give dihydropyrrole **10** {$[\alpha]_D^{25}$ + 64.4 (*c* 6.7, $CHCl_3$)} in 32% yield. Oxidation of **10** was accomplished using methyl(trifluoromethyl)dioxirane (TFMD)[21] in 1,1,1-trifluoromethylpropan-2-one and formation of nitrone **11** was observed by ^1H NMR [δ_H 6.97 (1 H, s)]. Exposure of the crude nitrone to dimethyl acetylenedicarboxylate (CH_2Cl_2, room temp.) gave a single cycloadduct **12** in 62% overall yield from dihydropyrrole **10**.† The assignment of *trans*-stereochemistry for the 2,5-disubstituted pyrrolidine subunit of **12** was based on a series of NOE difference experiments. Crucially, the enantiomeric integrity of **12** {$[\alpha]_D^{25}$ − 167.5 (*c* 7.5, $CHCl_3$)} has also been established. This was done by ^1H NMR analysis using (−)-Eu(tfc)$_3$, employing racemic **12** (prepared from racemic) as a standard. Racemic **12** showed two sets of signals for CH_2OCOBu^t, both methoxy groups, and the *tert*-butyl unit. In



Scheme 1 *Reagents and conditions*: i, Lawesson's reagent, THF, room temp.; ii, MeI, acetone, then aq. sat. $NaHCO_3$; iii, Raney Ni, acetone, reflux, 1 h; iv, MCPBA, CH_2Cl_2, 0 °C; v, heat or silica gel; vi, $KMnO_4$, Bu_4NBr or oxone, acetone; vii, $LiBH_4$, THF; viii, Bu^tCOCl, pyridine, DMAP; ix, TFMD, 1,1,1-trifluoropropan-2-one, −78 °C; x, dimethyl acetylenedicarboxylate, room temp.

the case of cycloadduct **12** derived from enantiomerically pure lactam **2**, no signals due to the other enantiomer were observed.

In conclusion, (*S*)-3,4-dihydro-2-pivaloyloxymethyl-2*H*-pyrrole 1-oxide has been synthesized from ethyl L-pyroglutamate and trapped as an enantiomerically pure 1,3-cycloadduct in high yield. Further cycloadditions directed to the synthesis of natural alkaloids are in progress.

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Footnote

† **12**: δ_H ($CDCl_3$, 400 MHz) 4.85 (1 H, t, *J* 6.1 Hz, H-3a), 4.19 (1 H, dd, *J* 11.3, 5.6 Hz, CH_2O), 4.15 (1 H, dd, *J* 11.3, 5.6 Hz, CH_2O), 3.85 (3 H, s, OCH_3), 3.72 (3 H, s, OCH_3), 3.56 (1 H, m, H-6), 2.30 (1 H, m, H-4β), 2.04 (1 H, m, H-4α), 1.92 (1 H, m, H-5α), 1.54 (1 H, m, H-5β), 1.15 (9 H, s, Bu^t); δ_C ($CDCl_3$, 62.5 MHz) 178.2 (CO_2Bu^t), 168.8 (CO_2Me), 162.6 (CO_2Me), 151.4 (C-2), 109.1 (C-3), 69.5/69.1 (C-3a/C-6), 64.8 (CH_2O), 53.1/51.8 (2 × OMe), 38.7 (CMe_3), 30.4/24.7 (C-4/C-5), 27.1 (CH_3).

The following NOE experiments were conducted: irradiation of H-3a (enhancement of H-4β); irradiation of H-4β (enhancement of H-4α, H-3a, H-5β); irradiation of H-5β (enhancement of H-5α, H-4β); irradiation of H-6 (enhancement of H-5α, H-4α).

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