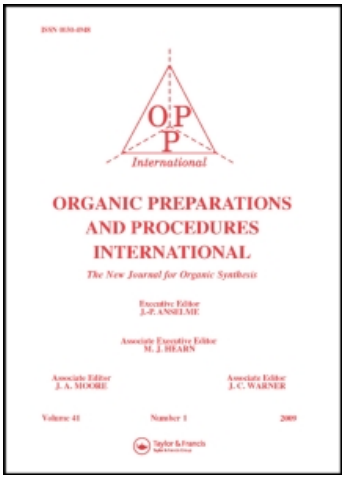

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AN IMPROVED ROUTE TO CYCLOALKA[b]PYRROLE 2-CARBOXYLATES

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OPPI BRIEFS

AN IMPROVED ROUTE TO CYCLOALKA[b]PYRROLE 2-CARBOXYLATES

Submitted by C. Balsamini, A. Bedini, G. Tarzia and A. Tontini*
(07/3/96)

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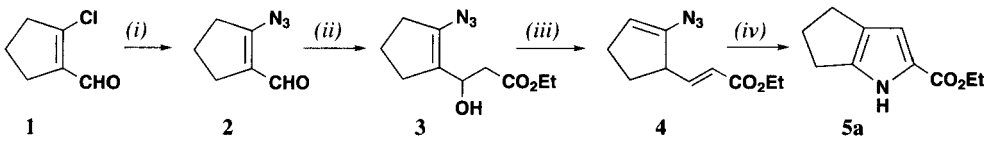
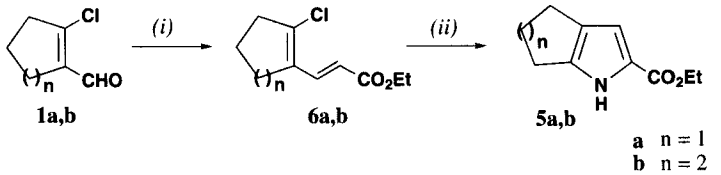
Cyclopenta- and cyclohexa[b]-pyrrole-2-carboxylate derivatives are key intermediates in the synthesis of angiotensin II antagonists[1] and of angiotensin converting enzyme inhibitors.[2] In the course of a project, we needed cycloalka[b]-pyrrole-2-carboxylates **5a** and **5b**. Thus we considered the synthesis of ethyl cyclopenta[b]-pyrrole-2-carboxylate **5a**[3] which is reported as involving condensation of active methylene aliphatic esters with the aldehyde group of the 2-azidocyclopent-1-ene-1-carbaldehyde **2**, followed by thermal cyclization *via* nitrene attack to the unsaturated side-chain. We have now achieved a two-step synthesis of **5a** (and of its cyclohexa analogue **5b**[4]) based on a modification of this literature method.[3]



1 2 3 4 5a

(i) NaN_3, DMSO, 10°; (ii) 1. LDA, THF, -78°; 2. CH_3CO_2Et; (iii) $POCl_3$, PhH, pyridine, 0°; (iv) Δ, xylene

Thus β-cycloalkenyl acrylates **6a,b** were easily prepared by a Wittig reaction of **1a,b** with ethoxycarbonylmethylene triphenylphosphorane which were then cyclized in one-step by heating in DMSO with sodium azide. In comparison with the former method, our procedure has the advantages of consisting of fewer steps (2 *vs* 4) and simpler and safer reaction conditions which avoid LDA at low temperature (-78°) and the isolation of the potentially explosive azide **2**.[5] Starting from **1a**, both methods gave **5a** in an identical overall yield (29%), whereas a 60% overall yield of **5b** was obtained from **1b**. This represents an improvement on the synthesis of **5b** from 2-formylcyclohexanone, where an isomeric mixture of alkyl cyclohexa[b]- and alkyl cyclohexa[c]pyrrole-2-carboxylate are obtained,[4,6] and provides an useful alternative to the methods for **5b** starting from 4H-2-oxazines.[7-9]



(i) $Ph_3P{=}CHCO_2Et$, PhH, rt (ii) NaN_3, DMSO, Δ

EXPERIMENTAL SECTION

Melting point were determined on a Buchi SMP-510 capillary apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian EM 60 spectrometer and are reported in ppm (δ) with TMS as the internal standard. EI-MS spectra (70eV) were taken on a Fisons TRIO 1000 instrument. ***Proper precautions should be used when working with azides.***

Ethyl β-(2-Chlorocyclopenten-1-yl)acrylate (6a) and Ethyl β-(2-Chlorocyclohexen-1-yl)acrylate (6b).- To the appropriate aldehyde **1a,b** (2 mmol)[10] dissolved in dry benzene (2 mL), was added ethoxycarbonylmethylene triphenylphosphorane (2 mmol); the strongly exothermic reaction mixture was stirred at room temperature (**1a**: 6 h; **1b**: 4 h). The solvent was evaporated and the residues were purified by flash chromatography (cyclohexane-EtOAc 8:2 as eluent) to give pure compounds as yellowish oils.

TABLE. β-Cycloalkenyl Acrylates **6a,b**

Cmpd	Yield (%)	MS (70eV) (mz,%)	^1H NMR ($CDCl_3$) (δ)
6a	99	200(16), 137(100)	7.60 (d, 1H), 5.75 (d, 1H), 4.25 (q, 2H), 2.9-1.8 (m, 6H), 1.30 (t, 3H).
6b	93	214(29), 151(100)	7.95 (d, 1H), 5.85 (d, 1H), 4.2 (q, 2H), 2.7-1.5 (m, 8H), 1.3 (t, 3H).

Ethyl Cyclopenta- and cyclohexa[b]pyrrole-2-carboxylate (5a,b).- To a solution of a suitable acrylate (**6a,b**, 1 mmol) in DMSO (1.4 mL), was added NaN_3 (1.5 mmol) and the mixture was heated (**6a:** 65°, **6b:** 105°) with stirring until the starting material had disappeared by TLC analysis (**6a:** 8 h; **6b:** 4h). The mixture was cooled, water (14 mL) was added, and the mixture was extracted with CH_2Cl_2; the organic phase was dried ($NaSO_4$), evaporated to dryness to give a tar. Flash column chromatography (cyclohexane-EtOAc 7:3 as eluent) furnished pure compounds (Yields: **5a** 29%; **5b** 64%). Compound **5a**: mp. 120-121° (cyclohexane), lit.[3] 124° (heptane). Compound **5b**: mp. 108-109° (Et_2O/light petr.), lit.[4] 98-100° (ethanol); the mass spectrum of **5b** is in agreement with the reported data.[4]

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SYNTHESES AND STEREOCHEMISTRY OF TETRAHYDROFURAN DERIVATIVES FROM α-PINENE

Submitted by (06/28/96)

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Tetrahydrofuran derivatives have been utilized as intermediates for the synthesis of α-haloesters[1,2] and γ-lactones[3] and terpenoid tetrahydrofuran derivatives have been useful as perfumes. Only a few papers have been reported the synthesis of terpenoid tetrahydrofuran derivatives.[4] In 1985, Kula[5] synthesized 2,2,5-trimethyl-3-(3-methyl-2-butenyl)tetrahydrofuran (**4b**) in several steps *via* diol **3b** derived from α–pinene (**1**) and found it to be endowed with good flowery-woody scent. However, the stereochemistry of **4b** was not investigated.

This paper reports a new one-pot method for the synthesis of a terpenoid tetrahydrofuran derivative (**4a**) *via* ozonization of α-pinene (**1**) and sodium borohydride reduction followed by treat-