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Synthesis of 3,4-fused cycloalkanopyrroles by 1,3-dipolar cycloaddition

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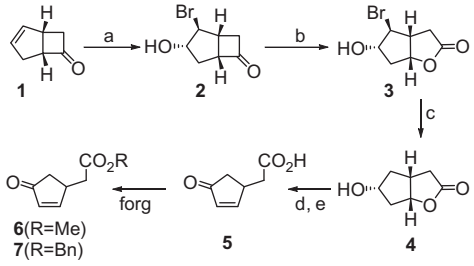
ABSTRACT

The synthesis of a number of 3,4-fused cycloalkanopyrroles bearing substituents on the cycloalkane ring was accomplished by 1,3-dipolar cycloaddition. The yield of the cyclization appeared to depend on the base-sensitivity of the Michael acceptor, but the method is applicable across a broad range of cyclic α,β-unsaturated ketone esters. Functional group transformations can be undertaken following pyrrole synthesis to increase the diversity of cycloalkanopyrroles accessible by this method. One pyrrole thus made is a diester of a conformationally-constrained analogue of porphobilinogen, the precursor of the natural tetrapyrroles.

3,4-Disubstituted pyrroles can be found in natural product alkaloids,[1,2] enzyme inhibitors,[3–6] fungicides,[7] pharmaceutical agents,[8] and modified tetrapyrroles and porphyrins,[9,10] as well as molecular catalysts[11] and electroluminescent materials.[12,13] These compounds are challenging targets, as modification of the β-positions of the pyrrole ring is difficult in the presence of the more reactive α-free positions.[14,15] Recent investigations have identified diverse multicomponent syntheses of pyrroles bearing substituents at both the 3- and 4-positions, including those for which the two substituents are contributed by the same reaction component,[16–20] and for which the two substituents are contributed by separate components.[21]

Pyrroles bearing cross-linked substituents at the 3- and 4-positions have been reported recently as assembly blocks for novel porphyrins[12,22] and as precursors to compounds of therapeutic interest,[5,6,17] but remain an underexplored synthetic target. Fused cycloalkanopyrroles of this class have typically been symmetrical[20,22] or simply substituted on the cycloalkane ring,[5,16,17] but there are few unsymmetrical, highly functionalized pyrroles of this class that we are aware of. These compounds represent appealing leads towards new chemotherapeutics and natural product analogues.

Multicomponent pyrrole syntheses offer the advantage of generating diverse families of related pyrroles from a single set of reaction conditions. Not all reactions show a high degree of functional group tolerance. One method that has been shown to be compatible with a range of functional groups is the 1,3-dipolar cycloaddition between isonitrile anions and Michael acceptors.[17,23–25] We have therefore prepared a number of cyclic Michael acceptors as precursors for the assembly of families of 3,4-fused cycloalkanopyrroles.



Scheme 1. Synthesis of cyclopentenone esters. Reagents and conditions: (a) NBS, Me_2CO/H_2O, 97%; (b) H_2O_2, AcOH, CH_2Cl_2, 90%; (c) Bu_3SnH, AIBN, PhMe, 57%; (d) DMSO, $(CF_3CO)_2O$, CH_2Cl_2, then NEt_3; (e) NEt_3, 69% over two steps; (f) K_2CO_3, MeI, DMF, 55%; (g) BnOH, DCC, DMAP, CH_2Cl_2, 63%.

Cyclopentenone ester **6** was synthesized in six steps from commercially available (±)-*cis*-bicyclo[3.2.0]hept-2-en-6-one (**1**) as described (without full experimental details) by Corey and Carpino[26] (Scheme 1) and the benzyl ester **7** was also made by esterification of cyclopentenone acid **5** with benzyl alcohol and DCC.

A second family of cyclic Michael acceptors was synthesised from 2-cyclopenten-1-one (**8**) (Scheme 2). The Wohl–Ziegler bromination of cyclopentenone **8**[27] was carried out in a 75% yield and the resulting bromide **9** was treated with anions of malonate diesters[28] to give cyclopentenone diesters **10**, **11** and **12**. Substitution reactions with dimethyl malonate were found to generate a significant proportion of a tetraester double addition product, formed by the overall displacement of bromide and conjugate addition by the malonate anion, but there was minimal double addition when the more sterically congested methyl *t*-butyl malonate and dibenzyl malonate were used.

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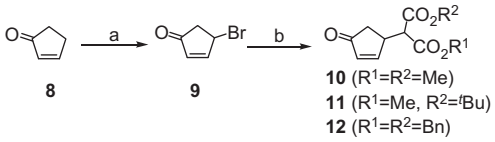


Scheme 2. Synthesis of cyclopentenone diesters for 1,3-dipolar cycloaddition. Reagents and conditions: (a) NBS, AIBN, CCl_4, 75%; (b) NaOMe, $R^1O_2CCH_2CO_2R^2$, MeOH/THF, 51% for **10**, 80% for **11**, 67% for **12**.

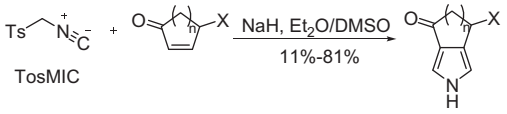
Cyclohexenone ester **16a** was prepared in near-quantitative yield from Danishefsky's diene (**13**) and methyl acrylate (**14a**) via a Diels–Alder reaction[29] (Scheme 3). The silyl enol ether adduct **15a** was converted, under acidic conditions at 0 °C,[30] into a mixture of unsaturated enones **16a** and **17a** in a 3:1 ratio. However it was possible to selectively convert **15a** into **16a**, the desired Michael acceptor, with zinc chloride in dichloromethane at room temperature.[31] Benzyl analogue **16b** was prepared in a 90% yield by a similar route from benzyl acrylate.

The cyclic α,β-unsaturated ketone esters were all tested (apart from **10**) as Michael acceptors for pyrrole formation by 1,3-dipolar cycloaddition. Reactions were carried out with *p*-toluene-sulfonylmethyl isocyanide (TosMIC) and sodium hydride in a 3:1 solution of diethyl ether and dimethyl sulfoxide at room temperature. The results are summarized in Table 1.

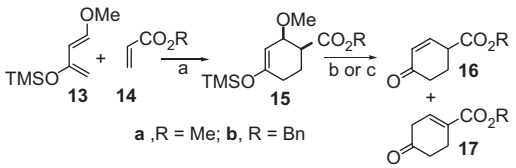
Esters **6** and **7** (entries 3 and 4) gave 3,4-fused bicyclic pyrroles in yields comparable to those obtained for cyclopentenone (**8**) itself and 2-cyclohexen-1-one (entries 1 and 2), which were themselves comparable to the literature reports.[17] In contrast, esters **12**, **16a** and **16b** were significantly poorer 1,3-dicycloaddition components (entries 6, 7 and 9) and gave yields of pyrroles of only 32%, 11% and 12%. It seems likely that the decrease in yield was a consequence of an acidic proton on the Michael acceptor, the proton adjacent to both the ester substituent and the alkene of **16a**/**b** and the proton adjacent to both ester groups in the case of **12**. However, diester **11** did give a more reasonable yield of 45%, despite its acidic proton. There was no significant difference in the yield of pyrrole from enone **16a** or from the mixture of enones **16a** and **17a** (entries 7 and 8).

We next demonstrated that the ketone group of the bicyclic pyrroles can be transformed into other functional groups of interest. It was necessary to activate the ketone towards nucleophilic addition by installing a *N*-tosyl group on the pyrroles. This was achieved by using sodium hydroxide and *p*-toluenesulfonyl chloride[33] (Scheme 4). A Horner–Wadsworth–Emmons reaction with *N*-tosyl pyrrole ketone **26** and triethyl phosphonoacetate gave the pyrrole diester **27** as a mixture of *E*- and *Z*-isomers. The reaction was difficult to drive to completion with sodium salt of the phosphonate, whereas the lithium salt, surprisingly, gave no detectable conversion. The tosyl group was cleaved with caesium carbonate[34] and the alkene was hydrogenated over palladium-on-charcoal to give unsymmetrically substituted cyclohexanopyr-

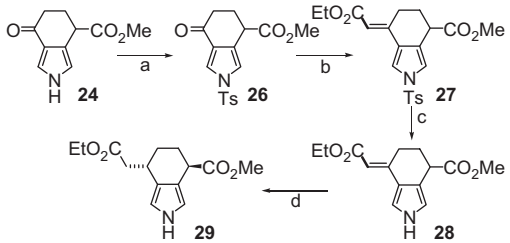
Table 1
Synthesis of 3,4-fused cycloalkanopyrroles[32]



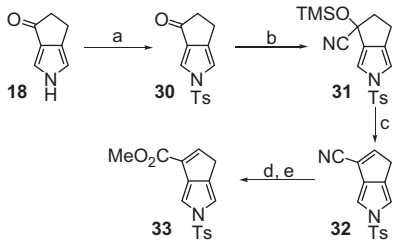
Entry	Michael acceptor	Pyrrole product	Yield (%)
1	**8**	**18**	72
2		**19**	42
3	**6**	**20**	81
4	**7**	**21**	57
5	**11**	**22**	45
6	**12**	**23**	32
7	**16a**	**24**	11
8	**16a**, **17a**	**24**	11
9	**16b**	**25**	12



Scheme 3. Synthesis of cyclohexenone compounds for 1,3-dipolar cycloaddition. Reagents and conditions: (a) PhMe, 91–99%; (b) 1 M HCl, THF, 72% for **16a** and 24% for **17a**; (c) $ZnCl_2$, CH_2Cl_2, 94–98% **16a**/**b**.



Scheme 4. Synthesis of an unsymmetrical pyrrole diester. Reagents and conditions: (a) NaOH, CH_2Cl_2, then TsCl, 59%; (b) $(EtO)_2POCH_2CO_2Et$, NaHMDS, THF, 47%; (c) $Cs_2CO_3{\cdot}2H_2O$, THF/EtOH, 53%; (d) H_2, Pd/C, EtOH, 99%.



Scheme 5. Single carbon homologation. Reagents and conditions: (a) NaOH, CH_2Cl_2, then TsCl, 97%; (b) TMSCN, TBAF, 39%; (c) *p*-TsOH, MeCN; 36%; (d) 6 M HCl, 1,4-dioxane; (e) $SOCl_2$, MeOH, 39% over two steps.

role diester **29** in a 15% overall yield from pyrrole **24**. Interestingly, diester **29** was found to be predominantly one diastereoisomer and the NOESY spectrum suggested that the two side-chains were *trans* oriented.

Diester **29** is an analogue of opsopyrrole dicarboxylic ester in which the side-chains at the 3- and 4-positions are linked by a $-CH_2CH_2-$ bridge, which conformationally constrains these side-chains. It is of interest, therefore, as a precursor of conformationally-constrained analogues of porphobilinogen (the monopyrrolic precursor) and the natural tetrapyrroles (e.g., uro-, copro- and proto-porphyrins and haem).

Single carbon homologation reactions of simple cyclopentanopyrrole ketone **18** proved to be more difficult. However, transformation of the ketone into an α,β-unsaturated ester **33** was achieved in four steps from *N*-tosyl pyrrole **30** in a 5% yield (Scheme 5). Addition of trimethylsilyl cyanide across the carbonyl bond was accomplished in the presence of tetrabutylammonium fluoride,[35] although the reaction was not as efficient as the corresponding treatment of pyrrole **18**. The silyl ether was eliminated by heating with *p*-toluenesulfonic acid in acetonitrile to give the α,β-unsaturated nitrile **32** in a 36% yield. Conversion into methyl ester **33** was achieved by hydrolysis of the nitrile under acidic conditions at 80 °C and esterification with thionyl chloride in methanol.[36]

In conclusion we have demonstrated that the 1,3-dipolar cycloaddition of the TosMIC anion to a variety of cycloalkenones is a practical route to families of cycloalkano[*c*]-pyrroles containing ester groups. These pyrroles can undergo various functional group transformations to enable the synthesis of a number of highly functionalized bicyclic pyrroles of interest.

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Supplementary data

Supplementary data (full experimental procedures and compound characterizations) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.013.

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32. *Typical procedure*: NaH (60% in mineral oil, 0.67 mmol) was washed with hexane under argon and then stirred at room temp in Et_2O (4 mL). A solution of cyclopentenone **6** (0.42 mmol) and TosMIC (0.45 mmol) in Et_2O/DMSO (4:2 mL) was added slowly. After 2 h the mixture was poured into H_2O (10 mL) and stirred for a further 20 min. Extraction and chromatography gave pyrrole **20** (81%) as an oil.
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