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Fused Cyclobutenomaleimides: Reactive Dienophiles for Molrac Construction

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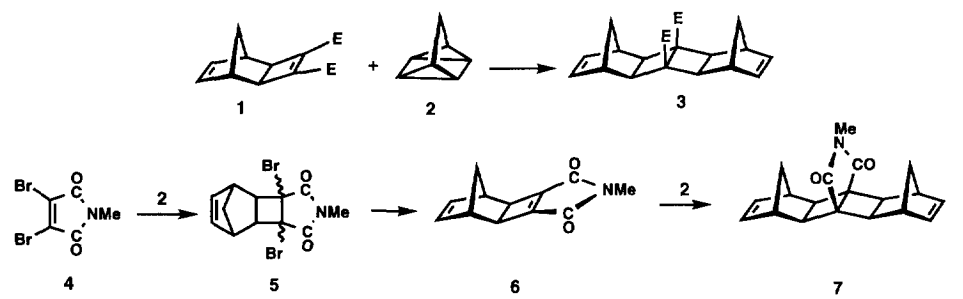
Abstract: The photoadducts derived from 3,4-dibromomaleimide and molrac olefines are debrominated (Zn/Ag) to provide highly dienophilic cyclobutenomaleimides fused to the rigid molrac framework; cycloaddition of cyclic dienes produces new molracs which are internally functionalised with succinimide bridges.

Molracs are emerging as important rigid frameworks for holding functionality in geometrically precise positions, and recent reports on their use in energy-transfer studies emphasise the role.[2] As part of a continuing program to develop new methods for introducing key functionality into such rigid alicyclic spacer systems,[3] we have investigated ways to provide succinimide bridges. Cyclobutenomaleimides, once considered too unstable for synthesis,[4] are now realised to be synthetic intermediates of bonafide existence.[5] In this communication we report on the role of cyclobutenomaleimides as intermediates in molrac construction.

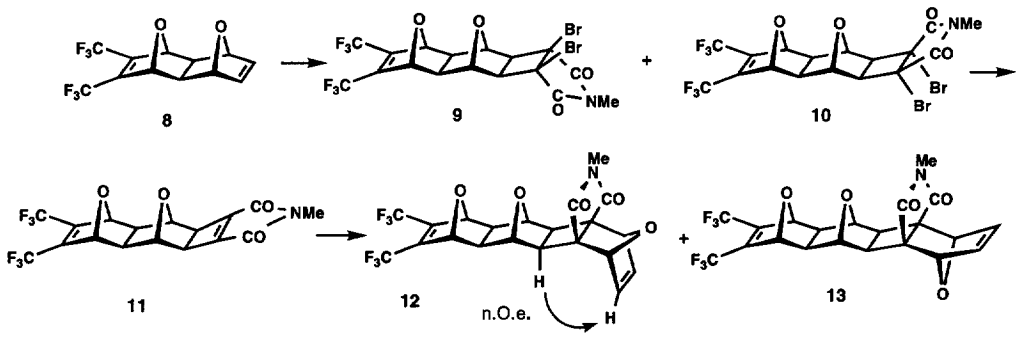
An integral step in the production of molrac rods containing in-frame ester substituents is the ability of cyclobutene 1,2-diesters, e.g. **1**, to react with quadricyclane **2** to form bishomo Diels-Alder adducts **3**.[6] We reasoned that preparation of the cyclobutenomaleimide **6** should provide access to molracs **7** where the succinimide bridge would allow the introduction of substituents precisely positioned on the molrac *via* attachment as a nitrogen substituent (Scheme 1). While the ester groups in **3** can be modified using standard FGI transformations, no success has been achieved in its conversion to **7.**



Scheme 1

Access to cyclobutenomaleimide **6** was achieved by debromination of the known adducts **5** (formed from the reaction of quadricyclane **2** with 3,4-dibromomaleimide **4**)[5] (Scheme 1). Treatment of this mixture with Zn/Ag couple (THF at reflux, 1 h) yielded the highly reactive cyclobutenomaleimide **6** (^{1}H NMR δ 1.25, dt J = 9.9, 1.2 Hz, 1H; 1.64, dp J = 9.9, 1.5 Hz, 1H; 2.78, p J = 1.8 Hz, 2H; 2.97, s, 3H; 3.18, bs, 2H; 6.25, t J = 1.8 Hz, 2H)[7,8] which could be isolated in crystalline form (m.p. > 360° C) following radial chromatography on silica (1:1 CH_2Cl_2, petroleum ether). Reaction of cyclobutenomaleimide **6** with quadricyclane **2** (60°C, 20 h) produced the molrac **7**, m.p. 178-180°C, in 42% yield.[10] The *exo,exo*-stereochemistry of **7** was assigned on the basis of the symmetry of the NMR spectrum (^{1}H NMR δ 1.16, brs, 4H; 2.33, s, 4H; 2.84, s, 3H; 3.07, brs, 4H; 6.06, t, 4H) which parallels the stereospecificity known to occur with Smith's diene **1** and quadricyclane.[6]

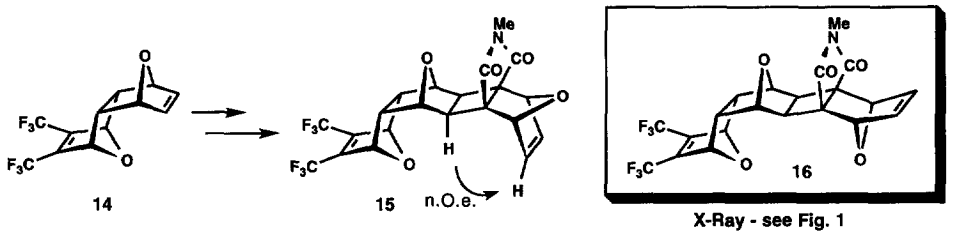
Cyclobutenomaleimide **6** is a highly reactive dienophile being activated by ring-strain from both the 4- and the 5-membered rings as well as electronically by the electron-withdrawing maleimide functionality. Accordingly, reaction with furan or cyclopentadiene occurs rapidly at room temperature, while reaction with hemicyclone is only conducted at reflux to promote formation of monomer from hemicyclone dimer rather than any reactivity concern with **6**. Single stereoisomers are produced from cyclopentadiene and hemicyclone, while two stereoisomers are obtained with furan.[11] The improved dienophilicity of **6** compared with **1** is apparent in the furan cycloaddition which only occurs with **1** in the presence of a Lewis acid.



Scheme 2

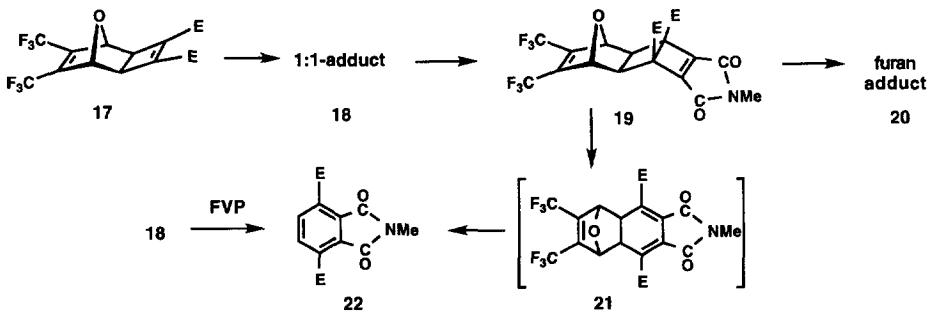
In order to prepare higher-order molracs it was necessary to find a reaction suitable for fusing cyclobutenomaleimides onto existing molrac olefins. This was achieved using a photochemical/debromination procedure (Scheme 2). Thus irradiation (1:1.03 ratio of **8**:**4** /acetone, 1hr, 450W hanovia lamp, pyrex filter) of 3,4-dibromomaleimide **4** in the presence of olefin **8** (used as a prototype for molrac 7-oxanorbornene) produces a mixture of [2π + 2π] cycloadducts **9** and **10** in a 1:1 ratio (yield 84%) which are debrominated ($Zn/TiCl_4$) to yield the unstable cyclobutenomaleimide **11**. Trapping of **11** with furan occurs efficiently to form a mixture (1:4) of cycloadducts **12** and **13** in 79% yield. Structural assignment in this case depends on chemical shift data for the *N*-methyl substituents; Alder adducts have higher field resonances than their *anti*-Alder isomers owing to the shielding effect of the 7-oxanorbornene π-bond (see table).

A similar sequence commencing with the *exo,endo*-isomer **14**[12] yields a mixture of molracs which contain the succinimide functionality (Scheme 3). The structure of the major isomer **16** has been established by X-ray crystallography (Fig. 1) and confirms that Alder *endo*-stereochemistry predominates in the cycloaddition step. The structure of the minor isomer **15** follows from n.O.e. studies.



Scheme 3

This photochemical/debromination sequence can also be conducted onto molracs where the terminus is a cyclobutene diester (Scheme 4). Reaction of the tricyclic diene **17** with 3,4-dibromomaleimide **4** (acetone, $\lambda > 225$ nm, 0°, 3 h) yielded a single 1:1-adduct **18** (m.p. 161-162°C, 45%). Debromination of **18** can be effected by treatment with Zn/Ag couple in THF at reflux. The resultant cyclobutenomaleimide **19** is too unstable to be isolated and is efficiently converted to the phthalimide **22** (m.p. 124-125°C) under the reaction conditions, presumably *via* the diene intermediate **21**. When conducted in the presence of furan, **19** can be trapped as adduct **20** (9%, m.p. 244-247°C) but again the major product is **22**. Phthalimide **22** can also be efficiently obtained from photoadduct **18** by FVP.



Scheme 4

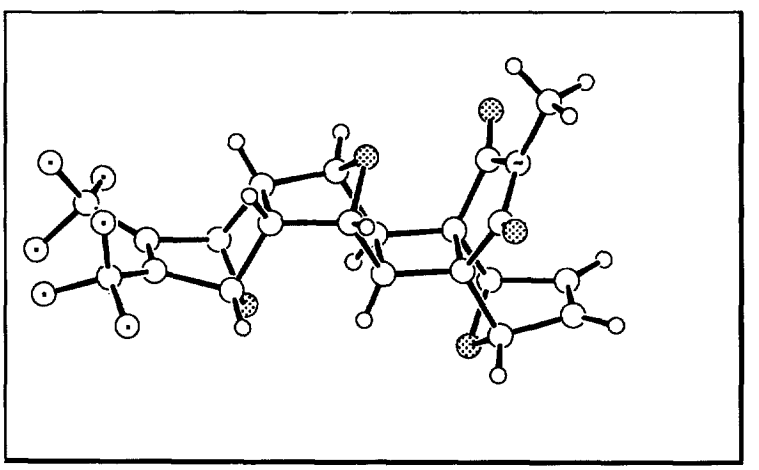


Fig. 1: X-Ray structure of compound **16**

References and Notes

1. Current address: Risk Assessment Section, Environment Standards Branch Protection Agency, Barton, ACT, Australia, 2600.
2. Kumar, K.; Tepper, R. J.; Zeng, Y.; Zimmt, M. B. *J. Org. Chem.* **1995**, *60*, 4051-4066 and references therein.
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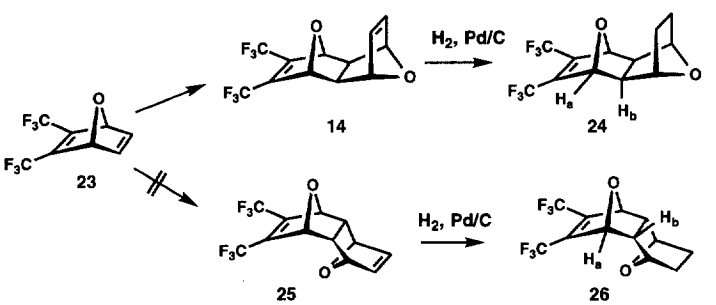
6. Warrener, R. N.; Pitt, I. G.; Butler, D. N. *J. Chem. Soc., Chem. Commun.* **1983**, 1340-1342.
7. One isomer of this mixture (presumably the one with the bromine substituents in the more accessible *anti*-fused site) debrominates faster than the other, but exact structures for these adducts have not been rigorously determined.
8. Compounds containing a THF moiety were also obtained in this reaction indicative of radical biproducts; precedent for this has been reported.[9]
9. Warrener, R. N.; Elsey, G. M.; Maksimovic, L.; Johnston, M.R.; Kennard, C. H. L. *Tetrahedron Lett.* **1995**, *36*, 7753-7756.
10. In this case the reaction was not stereospecific and a second isomeric product was obtained in 27% yield. This was not characterised.
11. *N*-Methyl resonances in the major isomers occur further upfield in the Alder adducts **13** and **16** reflecting the proximity of the double bond.

Structure	**12**	**13**	**15**	**16**
δ *N*-Me chemical shift	2.91	2.75	2.90	2.75

Table: ^{1}H NMR chemical shifts of succinimide *N*-methyl groups

12. ***Structure proof for compound 14.***
The structure of **14** was incorrectly assigned in our original report[13] of its preparation; the CF_3 groups were attached to the wrong π-bond, i.e. **25** rather than **14**. Structure **25** can be rejected on mechanistic considerations alone, as it involved attack of furan on the *endo*-face of its precursor, 7-oxanorbornadiene **23**. Both alternative structures incorporate the *exo, endo*-1,12-dioxatetracyclo[6.2.1.1.^{3,6}0.^{2,7}]deca-4,9-diene ring-structure; distinction requires unambiguous assignment of the CF_3-substituents. This was achieved by preparing the dihydro-derivative (**24** or **26**) by selective hydrogenation of the unsubstituted π-bond using H_2, Pd/C (Scheme 5). The resultant product has the downfield oxa-bridgehead resonance (H_a) occurring as a singlet which clearly supports **24** (and hence **14**) where the vicinal protons (H_b) have *endo*-stereochemistry (no coupling); in the alternative structure **26**, H_a would couple with the *exo*- H_b protons.



Scheme 5

13. Russell, R.A.; Longmore, R.W.; Weerasuria, K.D.V. Warrener, R.N. *Aust. J. Chem.*, **1991**, *44*, 1341-1345.

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