Tetrahedron Letters, Vol 32, No 40, pp 5469-5472, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

DIASTEREOSELECTION IN THE INTRAMOLECULAR DIELS-ALDER REACTION OF *o*-QUINODIMETHANES.

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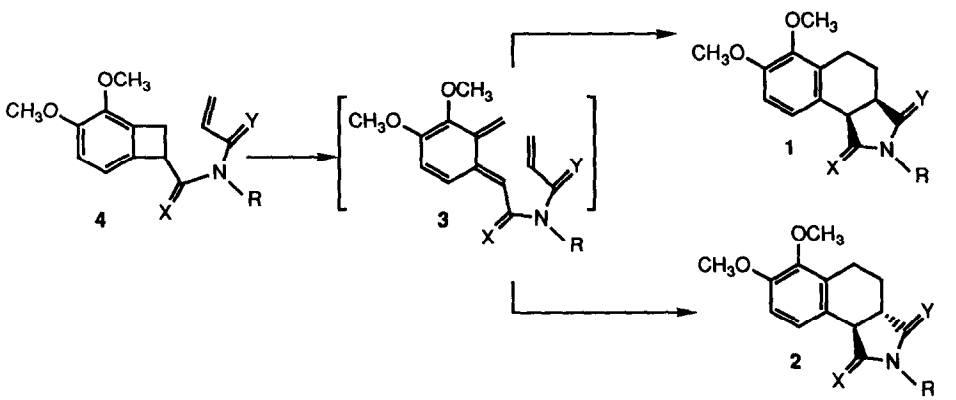
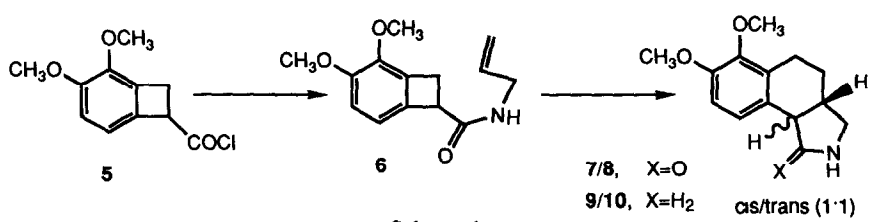
Abstract: An efficient diastereoselective synthesis of 2 is presented. A key feature is the intramolecular Diels-Alder reaction of o-quinodimethanes intermediates 3 derived from benzocyclobutenes 4 in which the exo-transition state is favored by incorporation of an amide functionality.

General routes for *cis* isoindolines **1** have been reported.[1] Herein we report a strategy for the preparation of *trans* fused isoindolines **2** based upon the intramolecular Diels-Alder reaction[2] of *o*-quinodimethane intermediates **3** derived from benzocyclobutenes **4**.



Oppolzer[3] and others[4,5] have studied the *endo/exo* selectivity in the cycloaddition reactions of *o*-quinodimethanes derived from benzocyclobutenes. We demonstrate here the possibility of directing intramolecular cycloaddition reactions towards either *endo* or *exo* products by modifying the diene or dienophile.

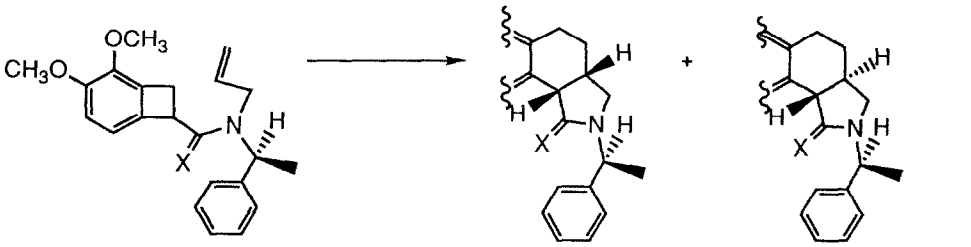


Scheme 1

As shown in Scheme **1**, an intramolecular Diels-Alder (DA) reaction is used as the key step for the construction of the B and C rings of the tetrahydrobenzisoindoline nucleus. The Diels-Alder precursor was synthesized starting from the known[6] benzocyclobutene acid chloride **5**. Thermolysis of the allyl-amide **6** in *o*-dichlorobenzene afforded the desired tricyclic amides **7** and **8**, as a (1:1) *cis/trans* mixture which could be easily separated by flash column chromatography. Reduction of the *cis* amide 7 with diborane afforded the isoindoline **9** in 78% yield. Similarly the *trans* amide **8** gave the corresponding *trans* isoindoline **10** in 81% yield.

An enantioselective method for the synthesis of isoindoline derivatives was desired. Since the Diels-Alder reaction afforded a mixture of *cis* (**7**) *o*-dichlorobenzene and *trans* (**8**) amides, we investigated the use of a chiral auxiliary to induce *exo/endo* diastereoselectivity and, preferably, facial selectivity to afford chiral induction. Compound **11d** was synthesized from the known benzocylobutene acid chloride **5** and (S)-*N*-allyl-α-methyl benzylamine[7] under standard conditions for amide formation.[8]

Thermolysis of compound **11d** in *o*-dichlorobenzene gave a 60:40 mixture of **12d** and **13d** diasteroisomers. However, no diastereoselectivity was observed in the intramolecular DA reaction of **11e** as shown in Scheme **2**



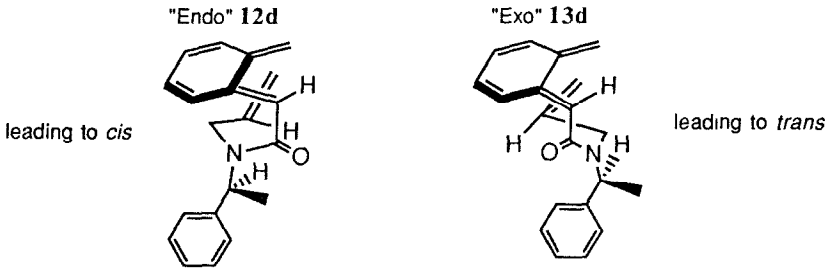
11d, X=O
11e, X=H_2

12d, X=O 60%
12e, X=H_2 50%

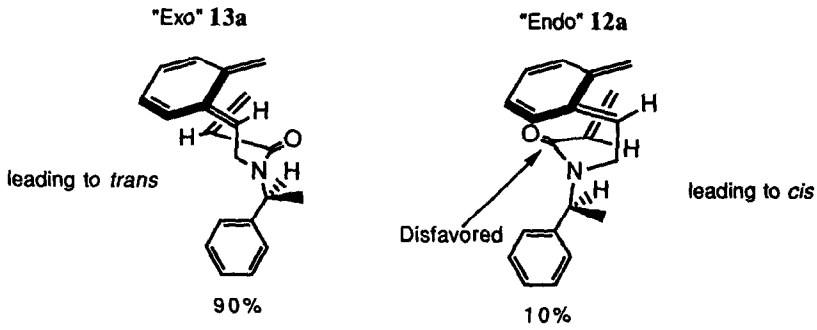
13d, X=O 40%
13e, X=H_2 50%

Scheme 2

Inspection of models, (Scheme **3**) revealed very little difference between the *exo* arrangement (conformer) leading to the *trans* isomers **13d** & **13e** and the *endo* arrangement leading to the *cis* isomers **12d** & **12e**. However, our analysis suggested that the transposition of the amide carbonyl as illustrated for the *endo/exo* pair would greatly favor cycloaddition via the *exo* transition state, thus achieving diasteroselection, as shown in Scheme **4**



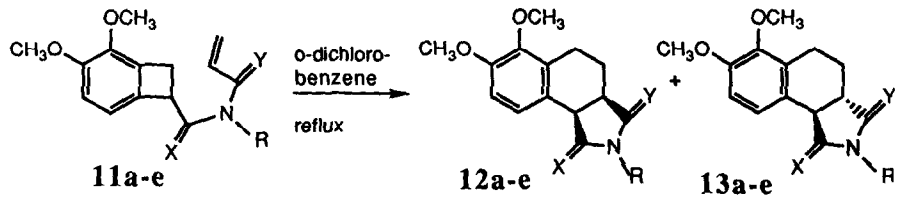
Scheme 3



Scheme 4

Indeed thermolysis of compound **11a** proceeded with a high degree of selectivity to afford a 90% yield of the desired *trans* isomer **13a**. The thermolysis of compound **11b** (R= benzyl or H), where the chiral auxillary is absent, gave a 1:1 mixture of the *cis* fused **12b** or **12c** and *trans* isomers **13b** or **13c**. Work is in progress using alternative chiral auxillaries to achieve face selectivity and thereby induce chirality.

Table 1: THERMOLYSIS OF BENZOCYCLOBUTENE DERIVATIVES



Entry	X	Y	R	% 12	% 13
a	H_2	O	(S)–α-methyl benzylamine	10	90
b	H_2	O	Benzyl	30	70
c	H_2	O	H	50	50
d	O	H_2	(S)–α-methyl benzylamine	60	40
e	H_2	H_2	(S)–α-methyl benzylamine	50	50

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7. (S)-*N*-allyl-α-methyl-benzylamine is prepared by alkylation of (S)-α-methyl benzylamine with allyl chloride in refluxing ethanol
8. Compound **11e** was synthesized in three steps in 87% yield starting from acid chloride **5** and (S)-α-methyl-benzylamine (1. Acylation, 2. reduction with diborane, 3. N-alkylation with allyl bromide).

(Received in USA 8 July 1991)