MEDIUM RING SYNTHESIS VIA INTRAMOLECULAR DIELS-ALDER
REACTION. 1. THE SYNTHESIS OF BICYCLO[6.4.0]DODECANE SYSTEMS

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Abstract. The regio- and stereocontrolled synthesis of cis-fused bicyclo[6.4.0]dodecane
ring systems by the application of the Lewis acid-catalyzed intramolecular Diels-Alder
reaction is described.

The synthesis of medium rings, particularly cyclooctanes, from acyclic precursors
continues to be a challenging problem in organic synthesis.[2] We wish to report that the
Lewis acid-catalyzed intramolecular Diels-Alder reaction[3] is extremely useful for cyclo-
octane synthesis and demonstrate its utility in regio- and stereocontrolled construction of
cis-fused bicyclo[6.4.0]dodecane systems 2 from simple acyclic precursors 1 (Scheme 1).[4]

SCHEME 1
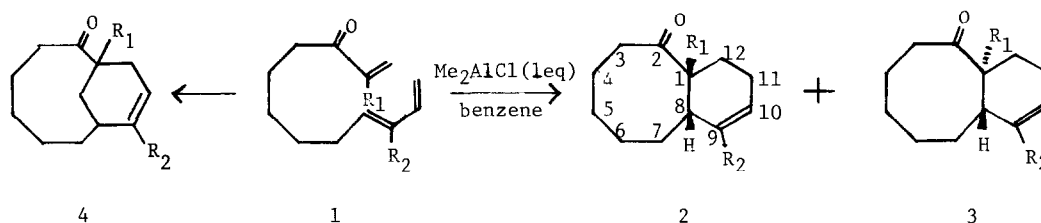
a : $R_1=R_2=H$,   b : $R_1=H$, $R_2=Me$,   c : $R_1=Me$, $R_2=H$,   d : $R_1=R_2=Me$

The four substrates 1a-d, readily available from 7,7-dimethoxyheptanal[6] (Scheme 2),
were employed and their uncatalyzed thermal reactions (~1.2 x 10^{-2} M in toluene/140°C/
degassed sealed tube) were first studied. The results were disappointing in that polymer
formation predominated in all cases.[7]

However, in the presence of Me_2AlCl as catalyst, 1a was smoothly converted at room
temperature to a single isolable product 2a[5] in 69% yield. Similarly, 1b-d were also
transformed, in each case, to a readily separable mixture of two products 2b-d (major) and
3b-d (minor), respectively (Table 1).[5] Upon base treatment (NaOMe/MeOH/25°C) 2a underwent
facile epimerization at C-1, providing a new compound 3a[5] (equilibrium ratio: 2a/3a =
1/32 by isolation). Likewise, 2b and 3b were interconverted under the basic conditions
(2b/3b = 1/1 by isolation). It should be noted, however, that all four pairs of compounds
(2a-d and 3a-d) thus obtained from 1a-d were found to be configurationally stable under the
Lewis acid conditions employed.[8]

Structurally, mass[5b] and ^{13}C NMR spectra clearly indicate that all products obtained

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SCHEME 2[a]

MeO ~~~~~~ CHO $\xrightarrow[\sim 39\%]{A}$ MeO ~~~~~~ R_2 $\xrightarrow[\sim 56\%]{B}$ __1a-d__
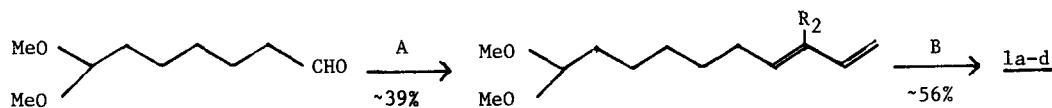
[a]Key. (A): ϕ_3PCHCO$_2$Me or ϕ_3PC(Me)CO$_2$Me/PhH/25°C; Dibal/CH$_2$Cl$_2$/-78°; PDC/DMF/0°C; Ph$_3$PCH$_2$/THF/0°C. (B): PyTsOH/(CH$_3$)$_2$CO, H$_2$O/Reflux; CH$_2$CHMgBr or CH$_2$C(Me)MgBr/THF/-78°C; TFAA/DMSO/CH$_2$Cl$_2$/-50°C, Et$_3$N/-50°C.

from __1a-d__ are monomeric cyloaddition products (Table 2). That these products have the bicyclo[6.4.0]dodecane framework (as in __2__ and __3__), not the alternative structure __4__, was indicated by the ^{1}H NMR spectra (obtained at either 300 or 600 MHz) which showed the presence of the partial structure =C(10)H-C(11)H$_2$-C(12)H$_2$- in all cases.[9] Additionally, for those compounds lacking angular substitution (i.e., R_1 = H), vicinal coupling between H$_1$ and H$_8$ was observed ($J_{1,8}$ = __2a__, 4.9 Hz; __3a__, 10.2 Hz; __2b__, 4.2 Hz; __3b__, 10.4 Hz).[9b] These observations confirm that each pair of compounds obtained from __1__ consists of the stereoisomers __2__ and __3__ in all four cases __a-d__.

Stereochemically, the relative magnitude of the $J_{1,8}$ values suggests that __2a-b__ and __3a-b__ are cis and trans, respectively. The validity of such a relationship in the bicyclo[6.4.0]-dodecane system was confirmed by chemically correlating __2a__ and __3a__ with authentic samples

TABLE 1. THE RESULTS OF THE CATALYZED REACTIONS			
Substrate	Reaction Temperature	Product Ratio[a] __2__ : __3__	Isolated Yield (__2__ + __3__)
__1a__	25°	~100 : ~0	69
__1b__	25°	89 : 11	62
__1c__	55°	83 : 17	74
__1d__	50°	74 : 26	69

[a]determined by isolation

cis-__5a__ and trans-__6a__, prepared via the intermolecular Diels-Alder reaction between cyclooct-2-en-1-one and butadiene under catalyzed[8a] and photochemical[10] conditions, respectively (Scheme 3). Similarly, __2c__ was correlated with authentic cis-__5c__ (Scheme 3) and hence __3c__ must be trans. Thus, the relative stereochemistry of the three pairs of compounds (__2a-c__ and __3a-c__) is solidly confirmed.

The stereochemistry of the remaining pair __2d__ and __3d__ was assigned as cis and trans, respectively, based on the ^{13}C chemical shift difference between the cis (__2a-d__) and trans (__3a-d__) series of compounds (Table 2). For example, in all cases C-2 is relatively shielded by 2.1 - 3.1 ppm in cis versus the corresponding trans isomer, and, when the angular methyl group is present (R_1 = Me), the methyl carbon atom is significantly deshielded by 7.2 - 8.3 ppm in cis versus trans (__2c__ vs. __3c__ and __2d__ vs. __3d__). These and other obvious trends[11] observed clearly justify the stereochemical assignment of __2d__ and __3d__, and hence confirm that the predominant product formed under the catalyzed conditions has, in each case studied (__a-d__), cis-fused bicyclo[6.4.0]dodecane structure __2__.[12]

TABLE 2: ^{13}CMR SPECTRA DATA^a OF THE PRODUCTS 2 AND 3

carbon^b	2a	3a	2b	3b	2c	3c	2d	3d
1	51.6(d)	51.2(d)	52.5(d)	53.0(d)	48.5(s)	48.9(s)	49.5(s)	49.6(s)
2	216.7(s)	219.5(s)	216.9(s)	220.0(s)	218.5(s)	220.9(s)	219.0(s)	221.1(s)
8	34.23(d)	40.1(d)	38.0(d)	42.0(d)	41.4(d)	36.4(d)	44.7(d)	39.4(d)
9	131.9(d)	131.8(d)	137.4(s)	135.8(s)	130.6(d)	131.1(d)	136.0(s)	134.7(s)
10	126.23(d)	125.9(d)	121.3(d)	122.7(d)	124.5(d)	125.2(d)	119.5(d)	121.5(d)
Me(1)^c					20.9(q)	12.6(q)	20.7(q)^d	13.5(q)^d
Me(9)^c			22.2(q)	21.7(q)			22.9(q)^d	23.8(q)^d

(a) Spectra were taken in CDCl$_3$ at 20.12 MHz. Chemical shifts are in ppm relative to TMS. Multiplicity is shown in parenthesis. (b) Only those carbons which are firmly assignable^{8a} are listed.^{9b} (c) Me(1) and Me(9) refer to the angular and allylic methyl carbon atoms, respectively. (d) The assignment was confirmed by selective proton decoupling experiments (see Footnote 4b for relevant protons).

In conclusion, we have demonstrated that the catalyzed intramolecular Diels-Alder reaction can be used to efficiently construct, with high regio- and stereoselectivity, vicinally fused cyclooctanes from readily available acyclic precursors.^{4,13} The application of this methodology to the synthesis of higher medium ring systems and natural products (e.g., ophiobolins) will be reported in due course.

SCHEME 3

a = R$_1$ = H
c = R$_2$ = Me
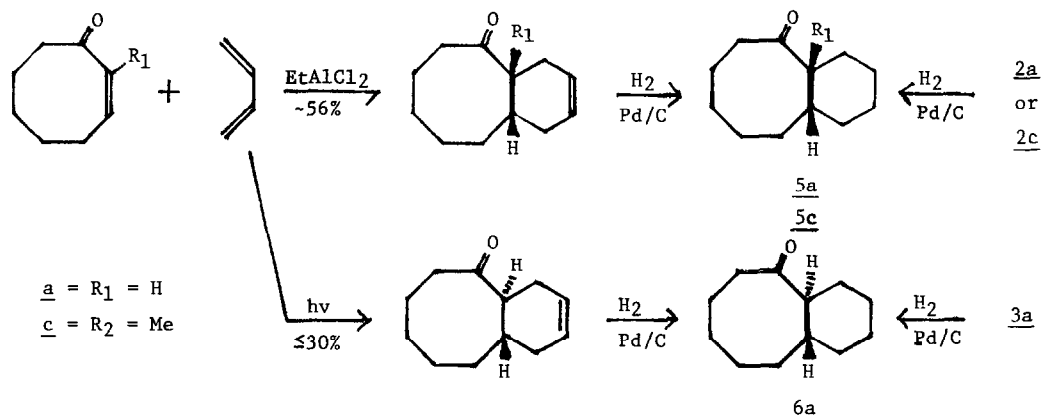
REFERENCES AND FOOTNOTES

1. IBM predoctoral research fellowship holder (1983–1984).

2. For example, see (a) G. Illuminati and L. Mandolini, Acc. Chem. Res. (1981), 14, 95; (b) R. L. Danheiser, S. K. Gee and H. Sand, J. Am. Chem. Soc. (1982), 104, 7670; (c) R. C. Gadwood and R. M. Lett, J. Org. Chem. (1982), 47, 2268 and reference cited therein; (d) L. A. Paquette, D. R. Andrews and J. P. Springer, J. Org. Chem. (1983), 48, 1147 and references cited therein.

3. For reviews, see (a) K. N. Houk, Acc. Chem. Res. (1975), 8, 361; (b) W. Oppolzer, Angew. Chem.Int. Ed. Engl. (1977), 16, 10–23; (c) G. Brieger and J. N. Bennett, Chem. Res. (1980), 80, 63–97; (d) W. R. Roush, H. R. Gillis and A. I. Ko, J. Am. Chem. Soc. (1982), 104, 2269 and references cited therein.

4. To our knowledge, the general utility of the intramolecular Diels-Alder reaction in the synthesis of bicyclo[6.4.0]dodecane systems has not been reported. However, two special cases are known: (a) K. Sakan and B. M. Craven, J. Am. Chem. Soc. (1983), 105, 3732; (b) K. N. Houk, (University of Pittsburgh), private communication.

5. (a) All new compounds reported were homogeneous by TLC and gave satisfactory IR, NMR and MASS spectra.
   (b) Selected data [MASS (m/e), IR (film) and ^{1}HNMR (CDCl$_3$)] of the cycloaddition products follow.
   2a: MASS 178(M^+), IR 1695 cm^{-1}, NMR δ 5.61 (m,2H);
   3a: MASS 178(M^+), IR 1698 cm^{-1}, NMR δ 5.65 (m,1H), 5.52 (m,1H);
   2b: MASS 192(M^+), IR 1703 cm^{-1}, NMR δ 5.32 (m,1H), 1.72 (s,3H);
   3b: MASS 192(M^+), IR 1699 cm^{-1}, NMR δ 5.45 (m,1H), 1.67 (s,3H);
   2c: MASS 192(M^+), IR 1704 cm^{-1}, NMR δ 5.57 (m,1H), 5.49 (m,1H), 1.05 (s,3H);
   3c: MASS 192(M^+), IR 1694 cm^{-1}, NMR δ 5.63 (m,1H), 5.31 (m,1H), 0.93 (s,3H);
   2d: MASS 206(M^+), IR 1697 cm^{-1}, NMR δ 5.24 (m,1H), 1.70 (m,3H), 1.02 (s,3H);
   3d: MASS 206(M^+), IR 1694 cm^{-1}, NMR δ 5.44 (m,1H), 1.67 (s,3H), 0.98 (s,3H).

6. This substance is readily available from cycloheptene by Schreiber's method: S. L. Schreiber, R. E. Claus and J. Reagan, Tetrahedron Lett. (1982), 23, 3867.

7. The substrates 1a and 1b gave, in low yields, a mixture of two monomeric cyloaddition products, 2a and 3a (1.75 : 1 by gc), and 2b and 3b (1 : 1.33 by gc), respectively, while 1c and 1d did not give such monomeric products. The products 2a-b and 3a-b were identical to those obtained via the catalyzed reactions of 1a-b (see text). The monomer yields were not improved by the addition of radical scavengers.

8. However, facile Lewis acid-catalyzed cis-trans isomerization was reported for the hydrindanone, octalone, decalone and hydrobenzosuberone systems when angular substitution was lacking. (a) F. Fringuelli, F. Pizzo, A. Taticchi, T. D. J. Halls and E. Wenkert, J. Org. Chem. (1982), 47, 5056 and references cited therein.

9. (a) The complex coupling pattern of the C-11 methylene protons under H$_{10}$ decoupled conditions clearly suggested the presence of an additional methylene group vicinal to the C-11 protons.
   (b) The detailed analysis of the NMR spectra will be reported later.

10. (a) P. E. Eaton and K. Lin, J. Am. Chem. Soc. (1964), 86, 2087. For a recent example, see (b) H. Shinozaki, S. Arai, and M. Tada, Bull. Chem. Soc. Japan (1976), 49, 821.

11. An additional clear trend is observed in the C-8 chemical shift which is sensitive to both the presence (or absence) of the angular methyl group and the ring juncture stereochemistry. Upon introduction of the angular substituent C-8 was considerably deshielded (by 6.7 – 7.1 ppm) in the cis-series (2a vs. 2c, and 2b bs. 2d), but shielded (by 2.7 – 3.8 ppm) in the trans-series (3a vs. 3c, and 3b vs. 3d . When angular substitution is lacking, C-8 is shielded (by 4.1 – 5.9 ppm) in cis relative to trans isomer (2a vs. 3a, and 2b vs. 3b). In contrast, when the substitution is present, the opposite trend (by 5.0 – 5.3 ppm) is apparent (2c vs. 3c, and 2d vs. 3d).

12. The observed cis-selectivity might be attributable to the enhanced secondary orbital interaction under the catalyzed conditions. See Ref. 2a and (a) D. Ginsburg, Tett. (1983), 39, 2095.

13. The application of the catalyzed reaction to the synthesis of bicyclo [5.3.1] undecane systems has recently been reported. K. J. Shea and J. W. Gilman, Tetrahedron Lett. (1983), 24, 657.