

DIELS-ALDER REACTIONS

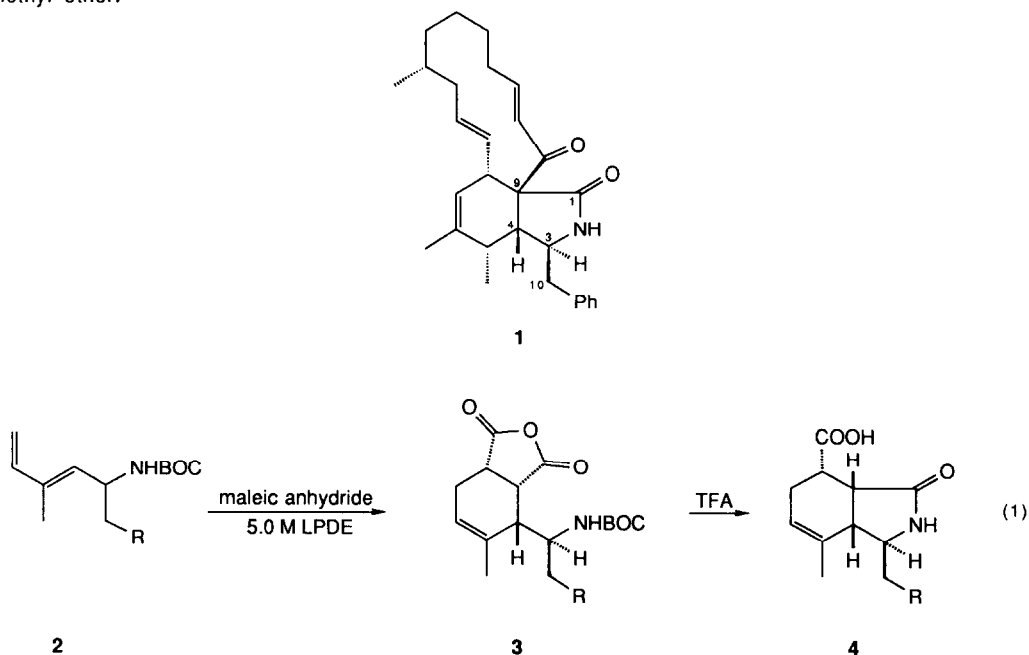
ENHANCED DIASTEREOFACIAL SELECTIVITY IN 5.0 M LiClO₄-Et₂O

APPROACH TO THE CONSTRUCTION OF THE ISOINDOLONE NUCLEUS OF CYTOCHALASANS

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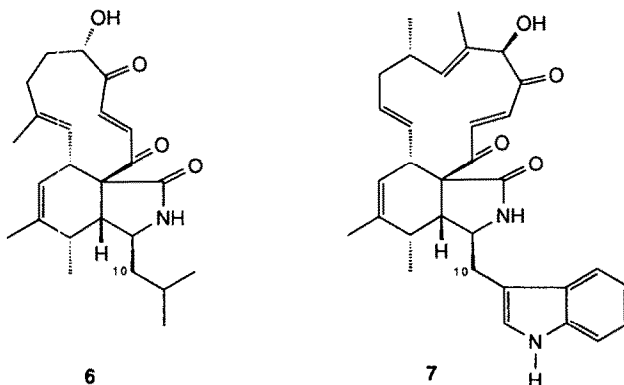
Abstract: Dienes of type **2** undergo highly diastereoselective Diels-Alder reactions with maleic anhydride in 5.0 M lithium perchlorate-diethyl ether giving rise to isobenzofurandiones which upon exposure to trifluoroacetic acid generate tetrahydroisindolones.

Medium effects can have a profound influence on the rate of organic reactions as illustrated by the remarkable rate accelerations observed for Diels-Alder reactions conducted in 5.0 M lithium perchlorate-diethyl ether.¹ In conjunction with an ongoing program in the cytochalasan area, we have developed a Diels-Alder strategy wherein an intact stereocenter adjacent to a diene unit is used to elaborate the tetrahydroisindolone nucleus of a variety of cytochalasans [cf. proxiphomin (**1**)] (Equation 1).² In addition we report that the diastereofacial selectivity, which is observed during the formation of cycloadduct **3** in conventional hydrocarbon solvents, can be enhanced by performing the Diels-Alder reaction in 5.0 M lithium perchlorate-diethyl ether.



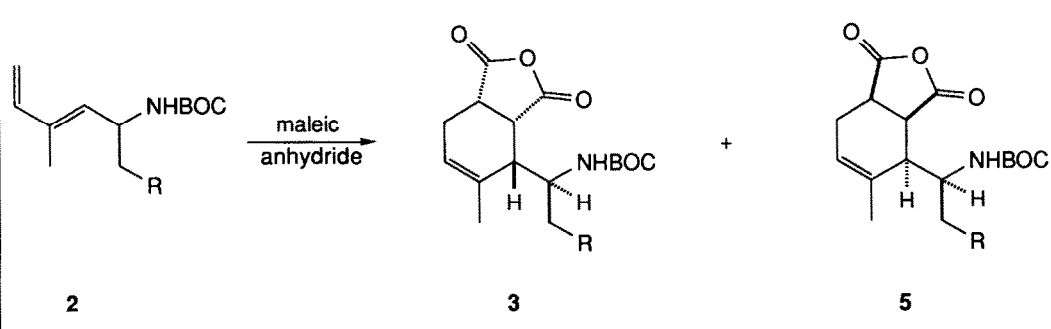
Our early studies in the cytochalasan area focused on a thermal Diels-Alder approach to elaborate the tetrahydroisoindolone nucleus. A 1.0 M solution of diene **2**³ (R = Ph) in toluene was found to react with 1.1 equiv of maleic anhydride at 55°C giving rise to isobenzofurandiones **3** (R = Ph) and **5** (R = Ph) in a ratio of 7.3:1.0 (Table 1). It was not surprising to find that when the reaction was conducted in toluene at 110°C, the diastereofacial selectivity was only 3.5:1.0. The reaction of maleic anhydride with **2** (R = Ph) in toluene proceeds very slowly at ambient temperature. In contrast, the reaction of **2** (R = Ph) with maleic anhydride in 5.0 M lithium perchlorate-diethyl ether proceeds rapidly at ambient temperature. Even more remarkable was our finding that in 5.0 M lithium perchlorate-diethyl ether the diastereofacial selectivity is enhanced to 15.6:1.0 (Table 1). The structures assigned to **3** (R = Ph), mp 188.0-189.5°C, and **5** (R = Ph) follow directly from a single crystal x-ray analysis of tetrahydroisoindolone **4** (R = Ph),⁴ mp 220-223°C, which was obtained in 80% yield by exposure of isobenzofurandione **3** (R = Ph) to 15 equiv of trifluoroacetic acid in ethyl acetate.

Whereas the cytochalasan, proxiphomin (**1**), features a phenyl group at C(10), the aspochalasans are characterized by the presence of an isopropyl group at C(10) [cf. aspochalasan B (**6**)] and the chaetoglobosons by the presence of an indol-3-yl group at C(10) [cf. chaetogloboson J (**7**)]. Thus we have prepared dienes of type **2**³ wherein R is isopropyl and an N-protected indol-3-yl group and examined their



reactions with maleic anhydride in both toluene at elevated temperatures and 5.0 M lithium perchlorate-diethyl ether at ambient temperature (Table 1). In both cases studied, enhanced diastereofacial selectivity was observed in the highly polar medium. Particularly noteworthy is the approximately five-fold increase in the diastereofacial selectivity (41.0:1 versus 3.5:1.0) observed for the Diels-Alder reaction of **2** (R = *i*-Pr)

Table 1. Diels-Alder Reactions of Diene 2 with Maleic Anhydride^a

						
entry	diene, R	solvent	temp, °C	time, h	ratio ^b 3:5	yield, ^c %
1	Ph	toluene	110	2	3.0:1.0	86
2	Ph	toluene	55	10	7.3:1.0	84
3	Ph	5.0 M LiClO ₄ -Et ₂ O	23	3	15.6:1.0	99
4	<i>i</i> -Pr	toluene	110	2	5.1:1.0	84
5	<i>i</i> -Pr	toluene	55	7	7.7:1.0	86
6	<i>i</i> -Pr	5.0 M LiClO ₄ -Et ₂ O	23	1.5	41.0:1.0	92
7 ^d	MBS-Ind ^e	toluene	110	2	3.5:1.0	85
8 ^d	MBS-Ind ^e	toluene	55	11	3.7:1.0	83
9 ^d	MBS-Ind ^e	5.0 M LiClO ₄ -Et ₂ O	23	2	12.7:1.0	80

^aAll reactions were conducted 1.0 M in diene in the presence of 1.1 equiv of maleic anhydride unless indicated otherwise. ^bRatios determined by ¹H NMR. ^cIsolated yield. ^dReaction conducted 0.3 M in diene. ^eN-*p*-methoxybenzenesulfonyl-3-indolyl.

with maleic anhydride when the reaction is conducted in 5.0 M lithium perchlorate-diethyl ether compared to toluene at elevated temperatures. In all cases examined the diastereofacial selectivity was eroded upon raising the temperature in toluene from 55°C to 110°C. The structures assigned to the major isobenzofurandiones **3** were confirmed by transformation (15 equiv TFA, EtOAc) (R = *i*-Pr or MBS-Ind) into the corresponding tetrahydroisindolones **4** (R = *i*-Pr), mp 192-193°C, and **4** (R = MBS-Ind), mp 161°C (dec).

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References

1. Grieco, P.A.; Nunes, J.J.; Gaul, M.D. *J. Am. Chem. Soc.*, **1990**, *112*, 4595. Also see Grieco, P.A. *Aldrichimica Acta*, **1991**, *24*, 59.
2. For previous synthetic approaches to cytochalasans, see: Thomas, E.J. *Acc. Chem. Res.*, **1991**, *24*, 229.
3. The dienes were prepared from the corresponding N-BOC aldehydes⁵ via a two-step sequence: addition of the Grignard reagent derived from 2-bromo-2-butene to the N-BOC aldehyde followed by a tandem sulfenate-sulfoxide [2,3] sigmatropic rearrangement/elimination sequence employing 2,4-dinitrobenzenesulfonyl chloride⁶ in 1,2-dichloroethane (reflux) containing triethylamine.
4. Compound **4** (R = Ph) crystallizes in space group P2₁/c with cell dimensions (at -155°C) of a = 10.115(4) Å, b = 8.431(3) Å, c = 17.155(7) Å, beta = 91.79(1); V = 1462.36 Å³, ρ calcd. = 1.296 (for Z = 4). A total of 2342 reflections were measured, of which 1276 were determined to be observable, F > 2.33 σ(F). All atoms were located and refined [R(F) = 0.0995 and R_w(F) = 0.0883].
5. The aldehydes were prepared according to the procedure of Rich: Rich, D.H.; Sun, E.T.; Boparai, A.S. *J. Org. Chem.*, **1978**, *43*, 3624.
6. Reich, H.J.; Wollowitz, S. *J. Am. Chem. Soc.*, **1982**, *104*, 7051.

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