Diels−Alder Reactions of Chiral 1,3-Dienes

Geoffrey T. Crisp* and Markus G. Gebauer

Department of Chemistry, The University of Adelaide, Adelaide 5005, South Australia

Received May 28, 1996[⊗]

Structurally related 1,3-dienes **3a**−**f** attached to a chiral carbon were treated with maleic anhydride under a variety of conditions. The initial Diels−Alder adducts were not isolated as they spontaneously rearranged to the isomeric isoindolones **6** and **7**. The rate of the rearrangement was dependent on the relative stereochemistry of the initial cycloadducts. The π-facial selectivity of the Diels−Alder reaction was determined by analyzing reaction mixtures of the isomeric isoindolones by ^{1}H and ^{13}C NMR spectroscopy and HPLC. A gradual increase in the π-facial selectivity was observed when the homoallylic hydroxyl group of the diene was endowed with a larger protecting group or slightly increased by performing the reactions in ether saturated with $LiClO_4$. These effects were rationalized by proposing a model based on 1,3-allylic strain in the transition state for the dienes **3a**−**f**.

1,3-Dienes are important intermediates in organic synthesis as they can be elaborated to six-membered carbocycles via a Diels−Alder reaction and up to four stereogenic centers can be formed in a single step.[1] The π-facial selectivity of 1,3-dienes that are attached to an adjacent asymmetric carbon atom has been explored in the synthesis of natural products,[2] and several studies have examined the parameters that govern this selectivity.[3] A greater understanding of these factors should lead to the design of 1,3-dienes that afford only a single diastereomer with the desired stereochemistry. High π-facial selectivity appears to be a feature of 1,3-dienes that possess a substituent in the *cis*-position,[4ab] although individual examples of high facial selectivity (>95:5) have been reported for dienes lacking this substituent.[4c] The steric interactions between the substituents on the adjacent stereogenic center and the *cis*-substituent are referred to as 1,3-allylic strain and must be minimized in order to obtain high diastereoselectivities.[5,6] Chiral 1,3-dienes that have a hydrogen atom in the *cis*-position usually display only a modest π-facial selectivity.[4a,b] In addition, both electronic and conformational effects can influence the π-facial bias[7] as well as the nature of the dienophile.[4c]

It was the purpose of this study to investigate the effect of varying the size of the homoallylic hydroxyl protecting group and the allylic amino group on the π-facial selectivity of a series of 1,3-dienes. Knowledge about these factors is expected to be useful when chiral 1,3-dienes are designed as intermediates in the synthesis of chiral natural products.

Results

The synthesis of dienes **3a**−**f** from **2a**−**f** and **1** is described in previous papers (Figure 1).[8,9] It was anticipated that a change to either the amino or hydroxyl protecting groups of dienes such as **3** would provide a means of varying the size of the substituents on the stereogenic carbon and therefore assess their resulting effect on the π-facial selectivity.

Diene **3a** was reacted with maleic anhydride in 1,2-dichlorobenzene (Figure 1, condition A). ^{1}H NMR analysis of the crude reaction mixture showed two sets of resonances that were assigned to the diastereomeric products **6a** and **7a** as described below. The IR spectrum of the crude mixture was consistent with a carboxylic acid and a tertiary cyclic imide. While isoindolone **6a** was isolated in 30% yield by HPLC, only a contaminated sample of the minor product **7a** could be obtained.

The reaction was then attempted using a concentrated solution of diene **3a** with maleic anhydride in refluxing CH_2Cl_2 (Figure 1, condition B). ^{1}H NMR analysis of the crude reaction mixture revealed the same predominant product **6a** as for the reaction conducted at 180 °C. The crude reaction mixture was extracted with saturated $NaHCO_3$, and the acidified extracts were purified by column chromatography to yield carboxylic acid **6a** in 47%. Maleic anhydride did not react with alkene **2a**, which suggested that the Diels−Alder reaction precedes the attack of the imine nitrogen on the anhydride, and therefore, an *intermolecular* Diels−Alder reaction had occurred and was followed by the rearrangement (Figure 1). It is also possible that a small amount of cycloadducts **6a** and **7a** formed initially and catalyzed the enolization of the carbamate group.[10]

* To whom correspondence should be addressed. E-mail: gcrisp@chemistry.adelaide.edu.au.

[⊗] Abstract published in *Advance ACS Abstracts,* November 1, 1996.

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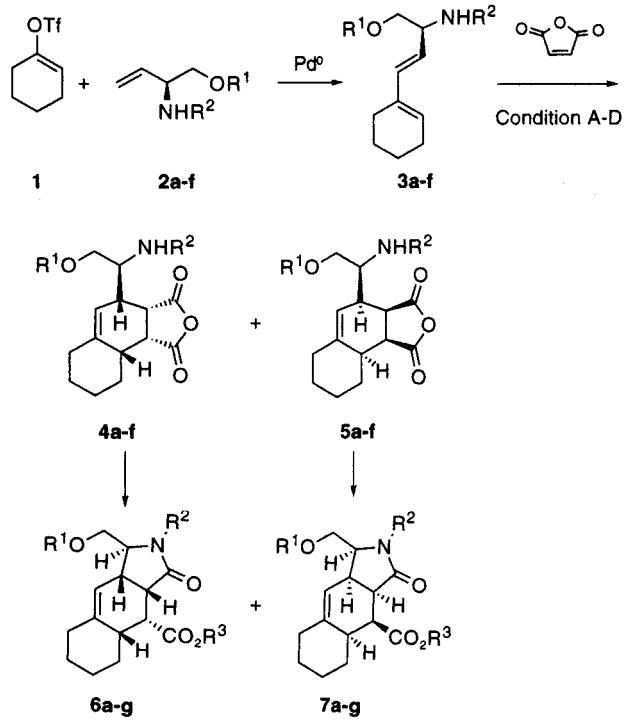
S0022-3263(96)00974-7 CCC: $12.00



a: R^1 = Ac, R^2 = Cbz, R^3 = H b: R^1 = H, R^2 = Cbz, R^3 = H

c: R^1 = CMe_3, R^2 = Cbz, R^3 = H d: R^1 = $SiMe_2$*t*-hexyl, R^2 = Cbz, R^3 = H

e: R^1 = $SiPh_2$*t*-Bu, R^2 = Cbz, R^3 = H f: R^1 = Ac, R^2 = Boc, R^3 = H

g: R^1 = Ac, R^2 = Cbz, R^3 = CH_3

A) maleic anhydride (3equiv), 0.03M of **3** in 1,2-dichlorobenzene, 180 ^{0}C, 1h
B) maleic anhydride (3equiv), 1.0M of **3** in dichloromethane, 40 ^{0}C, 12h
C) maleic anhydride (3equiv), 1.0M of **3** in chloroform-d, 25 ^{0}C, 4d
D) maleic anhydride (3equiv), 0.5M of **3** in $LiClO_4$ / Et_2O, 25 ^{0}C, 5h

Figure 1. Diels–Alder reactions of dienes **3a-f** with maleic anhydride.

To analyze the reaction mixture directly by ^{1}H NMR, the reaction of diene **3a** with maleic anhydride was conducted in $CDCl_3$ at 25 °C (Figure 1, condition C). Although isoindolone **6a** was the major product as before, the ratio of isomeric isoindolones **6a** and **7a** present in the crude product varied. It appeared that extended reaction times led to a decrease in the ratio of **6a** to **7a**. If the rearrangement of the cycloadducts **4a** and **5a** proceeded *at distinctly different rates*, then isoindolone **6a** would predominate due to the rapid rearrangement of the initial cycloadduct **4a** and a slow rearrangement of cycloadduct **5a** with time would lead to formation of **7a**.

To confirm this the Diels–Alder reaction of diene **3a** with maleic anhydride was monitored by HPLC (Figure 1, condition C). The initial ratio of **6a** to **7a** of 33.5:1.0 at 12 h was gradually reduced to 13.8:1.0 after 4 days. A late-eluting peak due to a nonpolar compound was also detected and decreased in intensity with time. When the reaction mixture was analyzed by ^{1}H NMR additional signals remained transiently after the starting diene **3a** was completely consumed. Presumably, a reaction intermediate such as the slowly rearranging cycloadduct **5a** had accumulated and gave rise to the late eluting peak in the HPLC traces. Refluxing the crude reaction product in 1,2-dichlorobenzene at 180 °C led to the disappearance of the late eluting peak. A quantitative analysis of the ratio of the sum of the peak areas in the chromatograms obtained after varying reaction times at 25 °C was performed. The ratio of isoindolone **7a** and its precursor **5a** with regard to isoindolone **6a** was constant. This constant relationship is consistent with a slow rearrangement of **5a** (which could not be isolated) as it accumulated during the reaction, while the isomeric **4a** rearranged too rapidly to be detected. The constant ratio of the peak areas was interpreted as the underlying π-facial selectivity of diene **3a** during the Diels–Alder reaction (de 56%).

Table 1. The Synthesis of Isoindolones 6 and 7 via the Diels–Alder Reaction of Dienes 3 with Maleic Anhydride

entry	diene	amino protecting group	hydroxyl protecting group	condns[a]	yield of **6** (%)	yield of **7** (%)	de[b] (%)
1	**3a**	Cbz	$COCH_3$	A	30	7[c]	46
2	**3a**	Cbz	$COCH_3$	B	47		nd[d]
3	**3a**	Cbz	$COCH_3$	C	38		56
4	**3a**	Cbz	$COCH_3$	D	42		69
5	**3b**	Cbz	none	C	nd[d]		nd[d]
6	**3c**	Cbz	$COCMe_3$	A	36	9	54
7	**3c**	Cbz	$COCMe_3$	B	55		nd[d]
8	**3c**	Cbz	$COCMe_3$	C	44		65
9	**3d**	Cbz	$SiMe_2$-*t*-hexyl	A	34	15[c]	63
10	**3d**	Cbz	$SiMe_2$-*t*-hexyl	B	62		nd[d]
11	**3d**	Cbz	$SiMe_2$-*t*-hexyl	C	46		74
12	**3e**	Cbz	$SiPh_2$-*t*-Bu	A	39	11	64
13	**3e**	Cbz	$SiPh_2$-*t*-Bu	B	63		nd[d]
14	**3e**	Cbz	$SiPh_2$-*t*-Bu	C	48		76
15	**3e**	Cbz	$SiPh_2$-*t*-Bu	D	49		83
16	**3f**	Boc	$COCH_3$	C	18		57

[a] Reactions were performed under the conditions listed in Figure 1. [b] de = diastereomeric excess of **6** over **7** determined by NMR analysis of crude reaction mixtures. [c] Only partially purified. [d] nd = not determined.

A direct interconversion of isoindolones **6a** and **7a** was ruled out by heating isomerically pure **6a** at 180 °C in 1,2-dichlorobenzene. After the solvent was distilled, only unchanged **6a** was detected by ^{1}H NMR analysis of the crude material. This experiment also suggested that the Diels–Alder reaction was under kinetic and not thermodynamic control.

When the Diels–Alder reactions of other dienes (**3c–e**) bearing a Cbz amino protecting group but different hydroxyl protecting groups were investigated (Figure 1), a similar rate difference in the rearrangement of the intermediate cycloadducts **4c–e** and **5c–e** was observed. In contrast, *both* Boc-protected initial adducts **4f** and **5f** rearranged rapidly, which was evidenced by a ratio of isomeric isoindolones **6g** and **7g** which remained constant during the reaction.

With the exception of alcohol **6b** all isoindolones **6** were isolated isomerically pure by chromatography of the crude Diels–Alder products in yields ranging from 18 to 63% (Table 1). Although, on the basis of a ^{1}H and ^{13}C NMR analysis of the reaction mixtures, isoindolone **6b** was formed when diene **3b** was treated with maleic anhydride in $CDCl_3$ at 25 °C, the isolation of **6b** was thwarted by the presence of significant amounts of unidentified material. A pure reference sample of alcohol **6b** was synthesized by the acidic hydrolysis of the acetyl-protected isoindolone **6a** in 96% yield.

For the isolation of the minor Diels–Alder products **7**, dienes were reacted with maleic anhydride in refluxing 1,2-dichlorobenzene to increase the relative amount of **7** in the crude product. Among the isoindolones **7**, only the pivaloyl, and *tert*-butyldiphenylsilyl-protected adducts **7c** and **7e** were isolated pure in very modest yields of 9 and 11%, respectively. The acetyl- and the *tert*-hexyldimethylsilyl-protected isoindolones **7a** and **7e** were only partially purified due to the presence of unidentified impu-

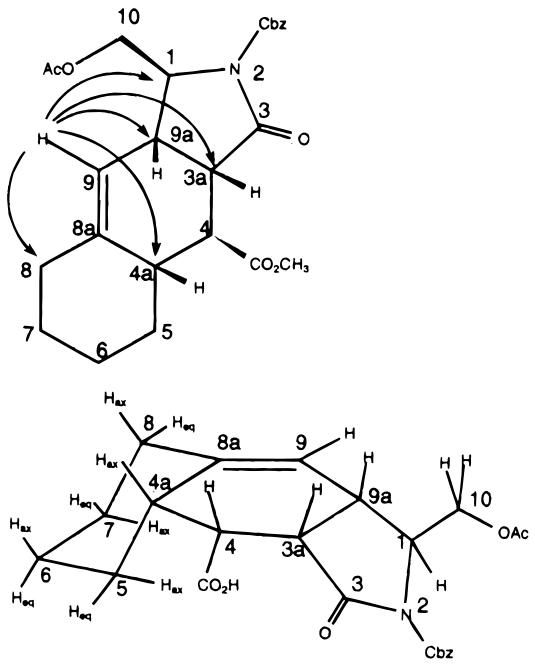


Figure 2. Stereochemistry of **6a**.

rities with identical retention times during chromatography on normal and reversed-phase silica.

The most remarkable structural feature of the isoindolones depicted in Figure 1 was their rigid cyclic structure, which was reflected in the appearance of the ^{1}H and ^{13}C NMR spectra. Isoindolones having the same relative stereochemistry displayed a great similarity in the ^{1}H and ^{13}C NMR data, as well as H,H COSY and H,C COSY spectra.

An interesting feature in the ^{1}H NMR spectra of isoindolones **6** was a small (J = 2 Hz) homoallylic proton coupling between H9a and H4a as well as H9a and H8$_{ax}$, which indicated a rigid collinear alignment of the H9a−C9a, H8$_{ax}$−C8, and H4a−C4a proton carbon bonds (Figure 2).[11] When the dihedral angle is near 90° no vicinal coupling may be observed.[12] This was indeed the case for the vicinal protons H1 and H9a of isoindolones **6** as evidenced by selective homonuclear decoupling experiments (detection limit: J = 0.5 Hz). On the contrary, a coupling of J = 7 Hz was measured for the same pair of protons (H1 and H9a) in the isomeric isoindolone **7**, which indicated a different relative stereochemistry.

As the connectivity between positions 1 and 9a of **6** could not be established via proton proton coupling, a COLOC experiment[13] was conducted. Cross peaks were observed between H9 and carbons in positions 1, 3a, 4a, 8, and 9a (Figure 2). Furthermore, H1 and C9a were correlated as well as one of the diastereotopic protons in position 10 with C9a. These results provided unambiguous proof of the connectivity between positions 1 and 9a of the methyl ester derivative **6g** for which no vicinal proton coupling was observed and allowed for a complete assignment of the ^{1}H and ^{13}C NMR spectra of **6**. The appearance of protons in positions 5, 6, 7, and 8 was independent of the stereochemistry and practically identical in all isoindolones. The assignment rested on NOE and decoupling difference spectroscopy.[14]

On the basis of Alder's *endo* rule,[15] both isoindolones **6a** and **7a** were expected to be derived from *endo* cycloadducts that only differed in the relative stereochemistry at C1 and C9a. Molecular models showed that only for the *trans*-isoindolones **6** was the dihedral angle spanned by H1 and H9a close to 90°. This suggested that the major product **6a** had the *trans*-stereochemistry depicted in Figure 1, while the minor product **7a** had the *cis*-stereochemistry (the terms "*trans*" and "*cis*" refer to protons H1 and H9a being on either opposite faces or on the same face of the five-membered ring). Unequivocal evidence for the stereochemical assignment of **7a** was obtained by the X-ray diffraction analysis of a single crystal of the methyl ester derivative **7g**,[16] which was obtained when the crude product of the reaction of diene **3a** with maleic anhydride in 1,2-dichlorobenzene (Figure 1) was esterified under neutral conditions with diazomethane in a yield of 74%. During the esterification no selective kinetic effects were observed since the two methyl esters **6g** and **7g** were produced in the same ratio as the parent carboxylic acids **6a** and **7a** (^{1}H NMR and HPLC). When a sample of the crude esters **6g** and **7g** was dissolved in a minimum amount of MeOH, crystals of **7g** precipitated. Purification of the mother liquor by HPLC resulted in the isolation of methyl ester **6g** in 21% yield. ^{1}H NMR analysis of this material confirmed that it was identical to the *major* compound present in the crude product of the esterification reaction.

The relative stereochemistry of ester **6g** was ascertained by steady-state NOE difference spectroscopy.[14,17] Selective irradiation of the diastereotopic protons in position 10 produced small but measurable NOE enhancements of less than 1% for H9a and for H3a. These NOEs suggested that the acetyl group and H9a and H3a were on the same face of the five-membered ring, which was consistent with the assignment of the *trans-endo*-stereochemistry to **6g**. NOE enhancements of less than 1% that were complementary to those measured in the previous experiment were observed for H10 when H3a or H9a of **6g** were selectively irradiated. The absolute stereochemistry of isoindolones **6a, 7a, 6c**, and **7** was predetermined by the (*S*) configuration of C2 in dienes **3**. The stereochemical assignment was extended to all isoindolones, which had very similar ^{1}H and ^{13}C NMR spectra.

The complete conversion of the starting dienes (**3a**−**f**) was ensured by refluxing the crude products in 1,2-dichlorobenzene for 1 h. Thereafter, the ratios of *trans*- to *cis*-isoindolones were interpreted as a measure for the π-facial selectivity of the respective dienes. As a single exception the de of the Diels−Alder reaction of the unprotected diene **3b** was not determined since the reaction mixture decomposed significantly.

In the case of the acetyl- and pivaloyl-protected isoindolones **6c** and **7c** this ratio was measured by ^{1}H NMR spectroscopy. This method of analysis could not be extended to silyl ether-protected isoindolones **6d** and **7d**

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as the corresponding proton signals, as well as those of **6e** and **7e**, were overlapping, and HPLC analysis proved unsuccessful. However, the tertiary olefinic resonances of **6d** and **7d** were well separated by approximately 4 ppm in both cases.

Several trends concerning the π-facial selectivity of dienes in the Diels−Alder reaction with maleic anhydride can be seen in Table 1. Larger hydroxyl protecting groups led to a gradual increase in the π-facial selectivity of the Diels−Alder reaction. In particular, the acetyl-protected diene **3a** had a lower π-facial selectivity than the pivaloyl-protected diene **3c** (Table 1, entries 3 and 8). A plateau of de ~75% was reached with the very bulky silyl ethers **3d** and **3e** (Table 1, entries 11 and 14). These results clearly implicate the hydroxyl protecting group in the steric shielding of the 1,3-diene moiety. The nature of the alkyl portion of the carbamate protecting group appeared to have no influence on the π-facial bias of the investigated dienes, suggesting that the carbamate group was directed away from the site of reaction in the transition state (Table 1, entries 3 and 16). The π-facial selectivity of the investigated dienes deteriorated with an increase in the reaction temperature from ambient temperature to 180 °C, as is expected for a reaction conducted under kinetic control (entries 1 and 3). Nevertheless, a de of 64% for the reaction of the siloxy-protected diene **3e** indicated that the π-facial selectivity was still relatively high even at the elevated temperature (Table 1, entry 12). A change in the reaction solvent from $CDCl_3$ to a saturated ethereal solution of $LiClO_4$ led to a slight increase in the π-facial selectivity (Table 1, entries 14 and 15). Such a solvent effect has been previously reported.[19]

Discussion

Many publications on the Diels−Alder reaction of acyclic chiral dienes have appeared in the literature,[3−5,7] and several explanations for their π-facial selectivity have been advanced. Essentially all rationales focused on an identification of the factors that stabilize the conformations that are accessed by rotation of the allylic C2−C3 bond as this was expected to be a key determinant for the π-facial selectivity.

Fallis[7] proposed that conformations that allow for a stabilization of the emerging σ^*-orbital on the carbon adjacent to the allylic carbon (for example, C3 in diene **3a**) by hyperconjugation from a collinear carbon−carbon or carbon−hydrogen bond (C1−C2 or C2−H2 in diene **3a**) would be preferred. Stereoelectronic effects of the latter kind are referred to as the "Cieplak-effect".[20] For some substituted acyclic 1,3-dienes a different model was proposed by Prein.[5] These dienes are distinguished from those with a hydrogen at C4 by a ground-state preference for conformations that minimize 1,3-allylic strain. Arguably, the transition state conformation of these dienes in the Diels−Alder reaction is also subject to conformational control due to allylic strain.[6] NMR evidence[21] and recent *ab initio* molecular orbital calculations[22] revealed

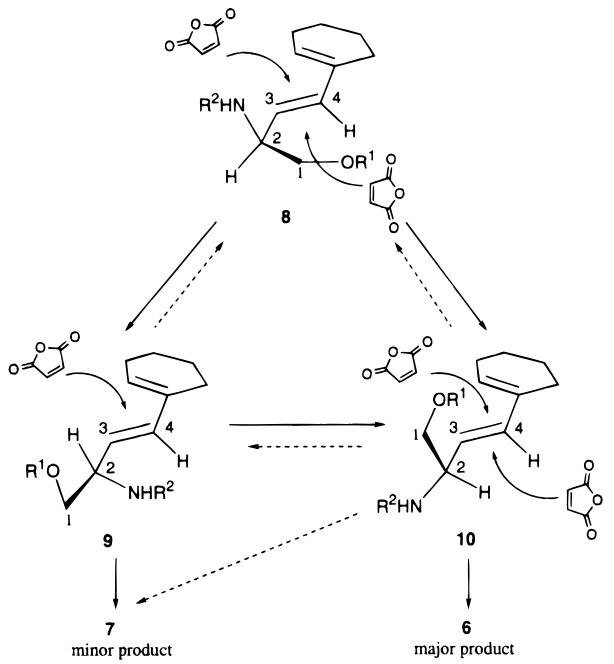

Figure 3.

that the *eclipsed* conformations of the carbon−carbon double bond with a substituent on the allylic carbon are generally lower in energy than the alternative staggered arrangements. Applying the literature results to dienes **3a**−**f** gives three ground-state conformations of low energy (Figure 3) by rotating the C2−C3 bond of dienes **3**. It is interesting to note that conformation **9** is essentially the solid-state conformation of diene **3a**.[23]

Assuming that the same order of stability is maintained in the transition state conformation of dienes **3** depicted in Figure 3,[6] minimizing 1,3-allylic strain predicts the correct stereochemistry for the major Diels−Alder products **6**. In the predominant conformer **10** in which 1,2- and 1,3-eclipsing interactions are minimized, one face of the planar diene unit was shielded against the approach of maleic anhydride by the hydroxyl protecting group, while the other face could be readily accessed leading to the formation of the major *trans*-isoindolone **6.** Since dienes **3a** and **3f** displayed the same π-facial selectivity (Table 1, entries 3 and 16) the amino protecting group was directed away from the diene unit. Furthermore, studies on CPK molecular models of diene **3a** indicated that the alkyl portion of the carbamate protecting group could not be located in the proximity of the diene unit without changing the hybridization of the imide nitrogen from sp^2 to sp^3 and introducing considerable strain into the molecule.

Diene conformation **9** would then give the minor *cis*-isoindolone **7**. Diene conformation **8**, on the other hand, was presumably least stable and therefore contributed only in a negligible way to the transition state, since significant nonbonding interactions between the CH_2OPg moiety and H4 existed.

Most importantly, this model based on the minimization of 1,3-allylic strain[5] and minimization of 1,2-eclipsing strain accounted for the observed increase in the π-facial selectivity with an increase in the size of the hydroxyl

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protecting group of dienes **3**. Small hydroxyl protecting groups, such as the acetyl of diene **3a**, could easily be in positions removed from the diene unit by a rotation around the C1−C2 bond. The hydrogen atoms in position 1 were too small to effectively shield the diene unit from an incoming dienophile in conformer **10**. However, even for the silyl ether-protected dienes **3d** and **3e** a plateau of de ~75% was approached as *both* diene conformations **9** and **10** contributed to the transition state. The alternative proposal based on stereoelectronic effects could not explain the trends observed in Table 1.[7,24]

When the Diels−Alder reaction of dienes **3a** and **3e** with maleic anhydride was conducted in ether saturated with $LiClO_4$, coordination and activation of the dienophile by lithium ions resulted and the effective size of the dienophile was increased. Conceivably, such an increase led to a better π-facial discrimination of conformation **10**, as the hydroxyl protecting group provided better shielding of the 1,3-diene moiety against the approach of a comparatively larger lithium-coordinated dienophile.

Conclusions

This study provided evidence that the π-facial selectivity of 1,3-dienes that have an attached stereogenic center can be enhanced (up to de = 83%) by increasing the size of the homoallylic protecting hydroxyl group in dienes **3** and conducting the reaction in $LiClO_4$/ether. A conformational model based on 1,3-allylic strain was proposed to rationalize the stereochemical outcome of the Diels−Alder reactions and the gradual increase in the π-facial selectivity of dienes **3** with progressively larger hydroxyl protecting groups.

Experimental Section

The synthesis of alkenes **2** and dienes **3** is reported separately.[8] Contaminating acid was removed from maleic anhydride by recrystallization ($CHCl_3$) and sublimation. All experiments were conducted under an atmosphere of nitrogen. HPLC was carried out on a reversed-phase C18-silica column (25 cm × 10 mm, particle size: 5 mm) at a flow rate of 4 mL/min using a 355:520:125:3 mixture of CH_3CN, H_2O, MeOH, and trifluoroacetic acid for the carboxylic acids or a 7:3 mixture of MeOH and H_2O for the methyl esters. Semipreparative HPLC was carried out under the same conditions using less H_2O in the solvent systems. The eluant was generally detected at 258 nm (Cbz derivatives) or at 240 nm (Boc derivatives). All NMR samples were analyzed as solutions in $CDCl_3$ at a static field strength of 300 MHz (for ^1H). For quantitative determination of carbon signals a concentrated sample (>70 mg) was analyzed in the presence of a few milligram of chromium(III) acetylacetonate. The pulse angle was 90° and the acquisition time 4 s. A radiationless delay of 2 s was included between scans. *No* window function was applied to the free induction decay signal. For NOE difference spectroscopy proton resonances were selectively irradiated for 0.8 s before each scan using a continous wave of weak power (5−25 mW) on the decoupler channel. A radiationless delay of 2 s was included. Typical parameters for COLOC experiments[13] were in the t_1-dimension (^1H) (spectral width = 2300 Hz; number of experiments = 180; number of data points = 512); in the t_2-dimension (^{13}C) (spectral width = 18 000 Hz; acquisition time = 0.17 s). The delay before the data acquisition was optimized for J = 8 Hz. H,H COSY[25] and H,C COSY[26] experiments were performed in a routine fashion and the data multiplied with a shifted sine-bell window.

Accurate isomeric ratios by ^{13}C NMR were obtained by minimizing NOE effects.[18] Proton decoupling was applied only during the acquisition time, and chromium acetylacetonate was added to suppress NOEs from protons onto carbon spins and to accelerate the relaxation of carbon spins. Under these conditions, the T_1 relaxation times of the tertiary olefinic ^{13}C spins were measured to be less than 200 ms, and a delay period of 2 s between scans was deemed adequate for a thermal equilibrium to re-establish.

(1*S*,3a*S*,4*R*,4a*R*,9a*S*)-1-(Acetoxymethyl)-2-*N*-(benzoxycarbonyl)-3-oxo-3a,4,4a,5,6,7,8,9a-octaahydrobenz[*f*]isoindole-4-carboxylic Acid (6a) (Figure 1, Condition B). A mixture of diene **3a** (600 mg, 1.747 mmol), activated 4A molecular sieves (707 mg), and maleic anhydride (514 mg, 5.241 mmol) in CH_2Cl_2 (5 mL) was refluxed for 1 d. A small aliquot of the reaction mixture was withdrawn, the solvent evaporated, and the residue analyzed by ^1H and ^{13}C NMR spectroscopy. Neither starting diene **3a** nor *cis*-isoindolone **7a** was detected, and resonances due to *trans*-isoindolone **6a** dominated the spectra. The reaction mixture was filtered, the molecular sieves were washed with CH_2Cl_2, the solvent was evaporated from the combined organic phases, and the residue was dissolved in ether (100 mL). It was extracted with ice-cold saturated $NaHCO_3$ (3 × 30 mL), and the combined extracts were immediately washed with ether (30 mL) and acidified by slowly adding concentrated HCl to pH = 0. The mixture was extracted with ether (3 × 50 mL), the combined extracts were dried ($MgSO_4$), and the was solvent evaporated to yield an amorphous light brown solid (531 mg, 69%). The crude product was analyzed by HPLC, and the following peaks were observed (relative intensities): t = 20.9 min (**6b**, 14%), t = 32.3 min (unknown, 8%), t = 33.8 min (**7a**, 2.5%), t = 35.3 min (unknown, 11%), t = 40.5 min (**6a**, 100%). The crude product was chromatographed on silica (120:120:12.5 hexane:CH_2Cl_2:AcOH) to yield **6a** (47%) as an oil: $[\alpha]^{25}_D = -61.8$ (*c*2.72, $CDCl_3$); IR (neat) 3300−2400, 1785, 1750−1730 cm^{-1}; ^1H NMR δ 13.2 (bs, 1 H), 7.42−7.33 (m, 5 H), 5.31, 5.26 (AB, J = 12 Hz, 2 H, Bn), 5.18 (bs, 1 H, H9), 4.43 (dd, J = 5, 12 Hz, 1 H, H10), 4.21 (dd, J = 4, 12 Hz, 1 H, H10), 4.13 (m, 1 H, H1), 3.65 (dd, J = 4, 8 Hz, 1 H, H3a), 3.01 (m, 1 H, H4), 2.91 (m, 1 H, H9a), 2.44 (m, 1 H, H4a), 2.23 (b, 1 H, $H8_{eq}$), 2.07 (s, 3 H, CH_3), 2.0 (m, 2 H, $H5_{eq}$, $H8_{ax}$), 1.8 (bs, 2 H, $H6_{eq}$, $H7_{eq}$), 1.4 (m, 1 H, $H7_{ax}$), 1.3 (m, 2 H, $H5_{ax}$, $H6_{ax}$); ^{13}C NMR δ 175.6, 175.0, 170.5, 151.1, 146.2 (C8a), 134.9, 128.6, 128.5, 127.9 (Ar), 116.6 (C9), 68.6 (Bn), 63.9 (C10), 61.6 (C1), 43.2 (C4), 40.4 (C3a), 38.6 (C4a), 36.6 (C8), 36.4 (C9a), 31.6 (C5), 29.0 (C7), 26.9 (C6), 20.8 (CH_3). Anal. Calcd for $C_{24}H_{27}NO_7$: C, 65.29; H, 6.16; N, 3.17. Found: C, 64.97; H, 6.40; N, 2.96.

(Figure 1, Condition D). A mixture of diene **3a** (62 mg, 0.181 mmol), $LiClO_4$ (213 mg, 2.00 mmol), and maleic anhydride (53 mg, 0.544 mmol) in dry ether (0.40 mL) was stirred in a sealed vessel at rt for 5 h until none of the starting diene **3a** was detected by TLC analysis (2:3 EtOAc:hexane). Ether (8 mL) and 1 M HCl (3 mL) were added, and the mixture was thoroughly shaken. The separated aqueous phase was extracted with ether (2 × 5 mL), the combined organic phases were washed with 1 M HCl (2 × 3 mL) and dried ($MgSO_4$), and the solvent was evaporated. The crude product was dissolved in 1,2-dichlorobenzene (5 mL) and heated at 180 °C for 1 h. Following distillation of the solvent (7 Torr), the ratio of **6a**:**7a** was 5.5 to 1.0 (^1H NMR). Chromatography of the crude reaction product afforded pure **6a** in 42% yield.

(1*S*,3a*S*,4*R*,4a*R*,9a*S*)-1-(Hydroxymethyl)-2-*N*-(benzoxycarbonyl)-3-oxo-3a,4,4a,5,6,7,8,9a-octahydrobenzo[*f*]isoindole-4-carboxylic Acid (6b) (Figure 1, Condition C). Diene **3b** (102 mg, 0.339 mmol) was treated with maleic anhydride (100 mg, 1.017 mmol) in $CDCl_3$ (0.5 mL) at rt for 24 h. Analysis of the crude reaction mixture by ^1H and ^{13}C NMR spectroscopy revealed the presence of **6b** as the major com-

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pound; however, other unidentified resonances were prominent in both spectra. An isolation of the major product **6b** was not attempted.

From 6a. Isoindolone **6a** (56 mg, 0.127 mmol) was dissolved in a mixture of methanol (6 mL), water (3 mL), and trifluoroacetic acid (1 mL) and stirred at rt for 10 h. The solvent was evaporated and the residue dissolved in CH_2Cl_2 (10 mL). The organic phase was washed with 1 M HCl (3 mL) and dried ($MgSO_4$) and the solvent evaporated to afford **6b** (45 mg) as a colorless oil in 96% yield: ^{1}H NMR δ 9.3 (bs, 2 H), 7.36 (m, 5 H), 5.32, 5.27 (AB, J = 12 Hz, 2 H, Bn), 5.18 (bs, 1 H, H9), 4.04−3.68 (m, 3 H, H10, H1), 3.80 (m, 1 H, H3a), 3.10 (dd, 1 H, H4), 2.98 (m, 1 H, H9a), 2.46 (m, 1 H, H4a), 2.22 (m, 1 H, $H8_{eq}$), 2.0 (m, 2 H, $H5_{eq}$, $H8_{ax}$), 1.8 (bs, 2 H, $H6_{eq}$, $H7_{eq}$), 1.4 (m, 1 H, $H7_{ax}$), 1.3 (m, 2 H, $H5_{ax}$, $H6_{ax}$); ^{13}C NMR δ 150.8, 145.9 (C8a), 117.4 (C9), 68.3 (Bn), 64.7 (C10), 62.8 (C1), 43.2 (C4), 40.6 (C3a), 38.5 (C4a), 36.4 (C8), 36.2 (C9a), 31.5 (C5), 28.9 (C7), 26.8 (C6). Anal. Calcd for $C_{22}H_{25}NO_6$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.77; H, 6.67; N, 3.60.

(1*S*,3a*S*,4*R*,4a*R*,9a*S*)-1-[(2′,2′-Dimethylethoxy)methyl]-2-*N*-(benzoxycarbonyl)-3-oxo-3a,4,4a, 5,6,7,8,9a-octahydrobenz[*f*]isoindole-4-carboxylic Acid (6c) (Figure 1, Condition C). A solution of diene **3c** (98 mg, 0.254 mmol) and maleic anhydride (75 mg, 0.763 mmol) in $CDCl_3$ (0.4 mL) was stirred at rt for 24 h. The solvent was evaporated and the residue dissolved in 1,2-dichlorobenzene (9 mL) and heated to reflux. The solvent was distilled (8 Torr) and the residue analyzed by ^{1}H NMR spectroscopy. A ratio of 4.65 to 1.0 for the proton resonances at δ = 3.71 ppm (**6c**) and at δ = 3.40 ppm (**7c**) was measured. Chromatography (120:120:12.5 hexane:CH_2Cl_2:AcOH) of the crude reaction product afforded **6c** in 44% yield as a colorless oil: ^{1}H NMR δ 12.9 (bs, 1 H), 5.33 (s, 2 H, Bn), 5.19 (bs, 1 H, H9), 4.46 (m, 1 H, H10), 4.20 (m, 1 H, H10), 4.16 (m, 1 H, H1), 3.60 (m, 1 H, H3a), 3.12 (dd, J = 4, 7 Hz, 1 H, H4), 2.90 (m, 1 H, H9a), 2.49 (m, 1 H, H4a), 2.23 (b, 1 H, $H8_{eq}$), 2.0 (m, 2 H, $H5_{eq}$, $H8_{ax}$), 1.8 (bs, 2 H, $H6_{eq}$, $H7_{eq}$), 1.4 (m, 1 H, $H7_{ax}$), 1.2 (m, 2 H, $H5_{ax}$, $H6_{ax}$), 1.17 (s, 9 H, CH_3); ^{13}C NMR δ 177.7, 177.5, 173.3, 150.6, 146.3 (C8a), 134.7, 128.7, 128.7, 128.0 (Ar), 116.5 (C9), 68.9 (Bn), 63.7 (C10), 61.2 (C1), 44.7 (C4), 40.6 (C3a), 39.0 (C4a), 38.8 (quarternary), 36.8 (C8), 36.5 (C9a), 31.6 (C5), 28.9 (C7), 27.1 (CH_3), 26.8 (C6). Anal. Calcd for $C_{27}H_{33}NO_7$: C, 67.06; H, 6.88; N, 2.90. Found: C, 66.72; H, 6.63; N, 2.59.

(Figure 1, Condition B). Diene **3c** (183 mg, 0.475 mmol) was treated with maleic anhydride (140 mg, 1.426 mmol) in refluxing CH_2Cl_2 (2.0 mL) in the presence of activated A4 molecular sieves (200 mg). After 12 h only a trace of diene **3c** was detected by TLC analysis of the reaction mixture (3:7 EtOAc:hexane), which was then cooled to rt. The molecular sieves were removed and washed with CH_2Cl_2. The combined organic phases were evaporated and the crude product chromatographed to yield **6c** (55%).

(1*S*,3a*S*,4*R*,4a*R*,9a*S*)-1-[[Dimethyl(1′,1′,2′-trimethylpropyl)siloxy]methyl]-2-*N*-(benzoxycarbonyl)-3-oxo-3a,4,4a,5,6,7,8,9a-octahydrobenz[*f*]isoindole-4-carboxylic Acid (6d) (Figure 1, Condition B). Diene **3d** (202 mg, 0.456 mmol) was treated with maleic anhydride (134 mg, 1.368 mmol) in CH_2Cl_2 as for **6c**. The crude product was chromatographed (140:100:12.5 hexane:CH_2Cl_2:AcOH) and **6d** obtained as a solid in 62% yield: mp 131−135 °C; $[\alpha]^{25}_D$ = −60.4 (*c* 3.86, CH_2Cl_2); ^{1}H NMR δ 13.0 (bs, 1 H), 5.35, 5.29 (AB, J = 12 Hz, 2 H, Bn), 5.19 (bs, 1 H, H9), 3.92 (m, 2 H, H10), 3.77 (m, 1 H, H1), 3.73 (m, 1 H, H3a), 3.10 (dd, J = 4, 6 Hz, 1 H, H4), 2.96 (m, 1 H, H9a), 2.46 (m, 1 H, H4a), 2.20 (m, 1 H, $H8_{eq}$), 2.0 (m, 2 H, $H5_{eq}$, $H8_{ax}$), 1.8 (bs, 2 H, $H6_{eq}$, $H7_{eq}$), 1.57 (sep, J = 7 Hz, 1 H, C*H*(CH_3)$_2$), 1.35−1.05 (m, 3 H, $H7_{ax}$, $H5_{ax}$, $H6_{ax}$), 0.87 (d, J = 7 Hz, 6 H, CH(C*H*$_3$)$_2$), 0.82 (s, 6 H, SiC(CH_3)$_2$), 0.06 (s, 6 H, Si(CH_3)$_2$); ^{13}C NMR δ 178.6, 174.3, 151.0, 145.5 (C8a), 134.8, 128.6, 128.6, 128.1 (Ar), 117.4 (C9), 68.6 (Bn), 64.9 (C10), 63.2 (C1), 45.1 (C4), 40.9 (C3a), 39.1 (C4a), 37.0 (C8), 36.5 (C9a), 34.0 (tertiary), 31.6 (C5), 28.8 (C7), 26.8 (C6), 25.0 (quaternary), 20.1, 20.1, 18.3, 18.3 (CH_3), −3.8 (Si(CH_3)$_2$). Anal. Calcd for $C_{30}H_{43}NSiO_6$: C, 66.51; H, 8.00; N, 2.59. Found: C, 66.16; H, 8.27; N, 2.49.

(Figure 1, Condition C). Diene **3d** (212 mg, 0.479 mmol) was treated with maleic anhydride (141 mg, 1.436 mmol) as for **6c**. After the distillation of 1,2-dichlorobenzene the remaining crude product and chromium(III) acetylacetonate (4 mg, 0.011 mmol) were dissolved in $CDCl_3$ (0.5 mL). The T_1 relaxation times of the resonances at δ =117.4 ppm (**6d**) and at δ = 113.0 ppm (**7d**) were estimated by the inversion recovery method. A ^{13}C NMR spectrum was acquired using inverse gated ^{1}H decoupling, and a ratio of 6.8:1.0 was determined for these resonances in favor of **6d**. Chromatography (140:100: 12.5 hexane:CH_2Cl_2:AcOH) of the crude reaction product afforded **6d** as a light red oil in 46%.

(1*S*,3a*S*,4*R*,4a*R*,9a*S*)-1-[(Diphenyl-*tert*-butylsiloxy)-methyl]-2-*N*-(benzoxycarbonyl)-3-oxo-1,3a,4,4a, 5,6,7,8,9a-octahydrobenz[*f*]isoindole-4-carboxylic Acid (6e). (Figure 1,Condition B). Diene **3e** (237 mg, 0.440 mmol) was treated with maleic anhydride (129 mg, 1.319 mmol) in CH_2Cl_2 as described previously for **6c**. The crude product was chromatographed (140:100:12.5 hexane:CH_2Cl_2:AcOH) and **6e** obtained as a colorless oil in 63% yield: IR (neat) 3300−2500, 1780, 1735, 1700 cm^{-1}; ^{1}H NMR δ 13.6 (bs, 1 H), 5.24 (dd, 2 H,), 5.19 (bs, 1 H), 3.91 (m, 2 H, H10), 3.83 (m, 1 H, H1), 3.79 (m, 1 H, H3a), 3.02 (m, 1 H, H4), 2.97 (m, 1 H, H9a), 2.45 (m, 1 H, H4a), 2.21 (m, 1 H, $H8_{eq}$), 2.0 (m, 2 H, $H5_{eq}$, $H8_{ax}$), 1.8 (bs, 2 H, $H6_{eq}$, $H7_{eq}$), 1.35−1.05 (m, 3 H, $H7_{ax}$, $H5_{ax}$, $H6_{ax}$), 1.07 (s, 9 H, CH_3); ^{13}C NMR δ 179.1, 173.7, 150.6, 145.6, 135.5, 135,4, 134.6, 132.5, 132.2, 130.2, 130.1, 128.7, 128.6, 128.0 (Ar), 117.2 (C9), 68.6 (Bn), 64.9 (C10), 64.0 (C1), 45.5 (C4), 41.0 (C3a), 39.1 (C4a), 36.9 (C8), 36.4 (C9a), 31.6 (C5), 29.7, 28.8 (C7), 26.8 (CH_3), 26.7 (C6). Anal. Calcd for $C_{38}H_{43}NSiO_6$: C, 71.56; H, 6.80; N, 2.20. Found: C, 71.47; H, 6.88; N, 2.19.

(Figure 1, Condition C). Diene **3e** (175 mg, 0.324 mmol) was treated with maleic anhydride (96 mg, 0.974 mmol) in $CDCl_3$ as for **6c**. Chromatography (140:100:12.5 hexane:CH_2Cl_2:AcOH) of the crude reaction product afforded **6e** in 48% yield as a light red oil.

(Figure 1, Condition D). Diene **3e** (156 mg, 0.289 mmol) was treated with maleic anhydride (85 mg, 0.867 mmol) in ether saturated with $LiClO_4$ as for **6a**. After 1,2-dichlorobenzene was distilled, the remaining crude product was analyzed by ^{13}C NMR spectroscopy in the presence of chromium(III) acetylacetonate as outlined for **6d** and showed a ratio of 11.0 to 1.0 for **6e** and **7e**. Chromatography (140:100:12.5 hexane: CH_2Cl_2:AcOH) of the crude reaction product afforded **6e** in 49% yield as a light red oil.

(1*S*,3a*S*,4*R*,4a*R*,9a*S*)-1-(Acetoxymethyl)-2-*N*-(*tert*-butoxycarbonyl)-3-oxo-3a,4,4a,5,6,7,8,9a-octahydrobenz[*f*]-isoindole-4-carboxylic Acid (6f). A solution of diene **3f** (116 mg, 0.375 mmol) and maleic anhydride (110 mg, 1.122 mmol) in $CDCl_3$ (0.40 mL) was stirred at rt. When the reaction mixture was analyzed by ^{1}H NMR after 4 h, the ratio of the resonances at δ = 4.45 ppm (**6f**) and at δ = 4.88 ppm (**7f**) was 3.6:1.0 in favor of **6f**. Analysis of the reaction mixture after 24 h revealed that this ratio had not changed. The residue was chromatographed (47:47:6 CH_2Cl_2:hexane:AcOH) to furnish **6f** as a solid (18%): mp 144−146 °C; $[\alpha]^{25}_D$ = −55.6° (*c* 0.65,CH_2Cl_2); IR (Nujol) 3200−2400, 1775, 1745, 1700 cm^{-1}; ^{1}H NMR δ 14.1 (bs, 1 H), 5.21 (bs, 1 H), 4.46 (dd, J = 5, 12 Hz, 1 H), 4.23 (m, 1 H), 4.08 (m, 1 H), 3.53 (dd, J = 4, 6 Hz, 1 H), 3.15 (dd, J = 4, 6 Hz, 1 H), 2.89 (m, 1 H), 2.50 (m, 1 H), 2.27 (m, 1 H), 2.10 (s, 3 H, C(O)CH_3), 2.0 (m, 2 H, $H5_{eq}$, $H8_{ax}$), 1.8 (bs, 2 H, $H6_{eq}$, $H7_{eq}$), 1.55 (s, 9 H, C(CH_3)), 1.4 (m, 1 H, $H7_{ax}$), 1.25 (m, 2 H, $H5_{ax}$, $H6_{ax}$); ^{13}C NMR δ 178.0, 173.9, 170.4, 149.0, 146.0 (C8a), 116.7 (C9), 84.9 (*C*(CH_3)), 68.1 (Bn), 63.8 (C10), 62.1 (C1), 45.2 (C10), 40.6 (C3a), 39.0 (C4a), 36.5 (C8), 36.3 (C9a), 31.6 (C5), 28.9 (C7), 27.9 (C(*C*H_3), 26.7 (C6), 20.4 (C(O)*C*H_3). Anal. Calcd for $C_{21}H_{29}NO_7$: C, 61.90; H, 7.17; N 3.44. Found: C, 61.59; H, 6.96; N, 3.36.

(1*S*,3a*R*,4*S*,4a*S*,9a*R*)-1-(Acetoxymethyl)-2-*N*-(benzoxycarbonyl)-3-oxo-3a,4,4a,5,6,7,8,9a-octahydrobenz[*f*]isoindole-4-carboxylic Acid (7a) (Figure 1, Condition A). A mixture of diene **3a** (500 mg, 1.456 mmol) and maleic anhydride (428 mg, 4.368 mmol) in 1,2-dichlorobenzene (50 mL) was refluxed for 1 h. An aliquot (5 mL) of the reaction mixture was withdrawn, the solvent distilled (7 Torr), and the residue analyzed by ^{1}H and ^{13}C NMR. No starting diene **7a** was detected, and resonances due to *trans*-isoindolone **6a** and *cis*-isoindolone **7a** dominated each spectrum. The ratio of the

resonances at δ = 3.57 ppm (**6a**) and at δ = 3.39 ppm (**7a**) was 2.6:1.0. The workup was the same as for **6a**. The crude products were purified by HPLC, and a partially purified sample of **7a** was isolated: ^{1}H NMR (incomplete) δ 13.3 (bs, 1 H), 7.42−7.33 (m, 5 H), 5.29 (dd, 2 H, Bn), 5.21 (bs, 1 H, H9), 4.87 (dd, J = 4, 11 Hz, 1 H, H10), 4.33 (ddd, J = 4, 7, 9 Hz, 1 H, H1), 4.19 (dd, J = 9, 11 Hz, 1 H, H10), 3.37 (m, 1 H, CH3a), 2.49 (m, 1 H, H4a), 2.24 (m, 1 H, H8$_{eq}$); ^{13}C NMR (incomplete) δ 112.0 (C9), 67.7 (Bn), 60.6 (C10), 56.8 (C1), 43.6 (C10), 41.1 (C3a), 38.0 (C4a), 36.6 (C8), 33.9 (C9a), 31.0 (C5), 28.6 (C7), 26.5 (C6), 20.7. From the main fraction pure **6a** was isolated in 30% yield.

(1*S*,3a*R*,4*S*,4a*S*,9a*R*)-1-[(2′,2′-Dimethylethoxy)methyl]-2-*N*-(benzoxycarbonyl)-3-oxo-3a,4,4a, 5,6,7,8,9a-octahydrobenz[*f*]isoindol-4-carboxylic Acid (7c) (Figure 1, Condition A). Diene **3c** (141 mg, 0.366 mmol) was treated with maleic anhydride (107.8 mg, 1.099 mmol) in refluxing 1,2-dichlorobenzene (12 mL) for 1 h. Chromatography (120:120:12.5 hexane:CH_2Cl_2:AcOH) of the crude product afforded **7c** as an oil in 9% yield: ^{1}H NMR δ 11.9 (bs, 1 H), 7.41 (m, 5 H), 5.31, 5.27 (AB, J = 12 Hz, 2 H, Bn), 5.12 (bs, 1 H), 4.76 (dd, J = 4,11 Hz, 1 H, H10), 4.39−4.26 (m, 2 H, H10, H1), 3.30 (dd, $J_{3a,9a}$=7 Hz, $J_{3,4}$=4 Hz, 1 H, H3a), 3.19 (dd, $J_{4,4a}$=7 Hz, $J_{4,3a}$=4 Hz, 1 H, H4), 3.08 (m, 1 H, H9a), 2.53 (m, 1 H, H4a), 2.24 (m, 1 H, H8$_{eq}$), 2.0 (m, 2 H, H5$_{eq}$, H8$_{ax}$), 1.8 (bs, 2 H, H6$_{eq}$, H7$_{eq}$), 1.4−1.1 (m, 3 H, H7$_{ax}$, H6$_{ax}$, H5$_{ax}$), 1.16 (s, 9 H, CH_3); ^{13}C NMR δ 178.6, 173.2, 151.3, 147.4 (C8a), 135.4, 128.7, 128.5, 128.5 (Ar), 111.8 (C9), 68.9 (Bn), 60.8 (C10), 57.8 (C1), 43.3 (C4), 41.4 (C3a), 38.9 (C4a), 38.9 (quaternary), 37.2 (C8), 35.0 (C9a), 31.4 (C5), 28.9 (C7), 27.1 (C6), 27.0 (CH_3). Anal. Calcd for $C_{27}H_{33}NO_7$: C, 67.06; H, 6.88; N, 2.90. Found: C, 66.89; H, 6.92; N, 2.77. From the main fraction pure **6c** was isolated in 36% yield.

(1*S*,3a*R*,4*S*,4a*S*,9a*R*)-1-[[Dimethyl(1′,1′,2′-trimethylpropyl)siloxy]methyl]-2-*N*-(benzoxycarbonyl)-3-oxo-3a,4,4a,5,6,7,8,9a-octahydrobenz[*f*]isoindole-4-carboxylic Acid (7d) (Figure 1, Condition A). Diene **3d** (168 mg, 0.379 mmol) was treated with maleic anhydride (112 mg, 1.138 mmol) as described for **7c**. The crude product was chromatographed (140:100:12.5 hexane:CH_2Cl_2:AcOH) and **7d** obtained as an oil (11%): ^{1}H NMR δ 14.3 (bs, 1 H), 7.35 (m, 5 H), 5.46 (bs, 1 H, H9), 5.25 (dd, 2 H, Bn), 4.29 (dd, J = 4, 10 Hz, 1 H, H10), 4.08 (ddd, J = 4, 6, 10 Hz, 1 H, H1), 3.64 (t, J = 10 Hz, 1 H, H10), 3.25 (dd, $J_{3a,9a}$=7 Hz, $J_{3,4}$=4 Hz, 1 H, H3a), 3.14 (dd, $J_{4,4a}$=7 Hz, $J_{4,3a}$=4 Hz, 1 H, H4), 3.05 (m, 1 H, H9a), 2.47 (m, 1 H, H4a), 2.19 (m, 1 H, H8$_{eq}$), 2.0 (m, 2 H, H5$_{eq}$, H8$_{ax}$), 1.8 (bs, 2 H, H6$_{eq}$, H7$_{eq}$), 1.57 (sep, J = 7 Hz, 1 H, C*H*(CH$_3$)$_2$), 1.4−1.1 (m, 3 H, H7$_{ax}$, H6$_{ax}$, H5$_{ax}$), 0.87 (d, J = 7 Hz, 6 H, CH(C*H*$_3$)$_2$), 0.83 (s, 6 H, SiC(CH$_3$)$_2$), 0.06 (s, 6 H, Si(CH$_3$)$_2$); ^{13}C NMR δ 178.5, 173.2, 151.0, 146.3 (C8a), 134.6, 128.7, 128.5, 128.4 (Ar), 113.0 (C9), 68.9 (Bn), 60.5 (C10), 59.5 (C1), 44.4 (C4), 41.5 (C3a), 39.1 (C4a), 37.1 (C8), 34.6 (C9a), 34.0, 31.5 (C5), 29.0 (C7), 27.0 (C6), 25.0, 20.1, 20.1, 18.3, 18.3 (CH_3), −3.7 (Si(CH$_3$)$_2$). From the main fraction pure **6e** was isolated in a yield of 34%.

(1*S*,3a*R*,4*S*,4a*S*,9a*R*)-1-[(Diphenyl-*tert*-butylsiloxy)methyl]-2-*N*-(benzoxycarbonyl)-3-oxo-3a,4,4a,5, 6,7,8,9a-octahydrobenz[*f*]isoindole-4-carboxylic Acid (7e). (Figure 1, Condition A). Diene **3e** (231 mg, 0.406 mmol) was treated with maleic anhydride (118 mg, 1.208 mmol) as described for **7c**. The crude product was chromatographed (140:100:12.5 hexane:CH_2Cl_2:AcOH) and **7e** obtained as an oil (11%): $[\alpha]^{25}_D$ = −3.26° (*c* 0.46,CH_2Cl_2); IR (neat) 3300−2500, 1795, 1760, 1730 cm^{-1}; ^{1}H NMR δ 13.8 (bs, 1 H), 7.65−7.25 (m, 15 H), 5.51 (bs, 1 H, H9), 5.10 (dd, 2 H, Bn), 4.45 (dd, J = 5, 10 Hz, 1 H, H10), 4.11 (m, 1 H, H1), 3.72 (t, J = 10 Hz, 1 H, H10), 3.28−3.18 (m, 2 H, H3a, H4, H9a), 2.52 (m, 1 H, H4a), 2.15 (m, 1 H, H8$_{eq}$), 2.0 (m, 2 H, H5$_{eq}$, H8$_{ax}$), 1.8 (bs, 2 H, H6$_{eq}$, H7$_{eq}$), 1.4−1.1 (m, 3 H, H7$_{ax}$, H6$_{ax}$, H5$_{ax}$), 1.07 (s, 9 H, CH_3); ^{13}C NMR δ 178.9, 173.4, 150.9, 146.7 (C8a), 135.5, 135.5, 134.3, 132.9, 132.8, 130.1, 130.0, 128.6, 128.4, 128.4, 127.9, 112.7 (C9), 68.9 (Bn), 60.4 (C10), 60.7 (C1), 45.0 (C4), 41.6 (C3a), 39.2 (C4a), 37.0 (C8), 34.7 (C9a), 31.6 (C5), 29.8, 28.8 (C7), 26.9 (C6), 26.9 (CH_3). Anal. Calcd for $C_{38}H_{43}NSiO_6$: C, 71.56; H, 6.80; N, 2.20. Found: C, 71.34; H, 6.81; N, 2.17. From the main fraction pure **6e** was isolated in 39% yield.

Methyl (1*S*,3a*S*,4*R*,4a*R*,9a*S*)-1-(Acetoxymethyl)-2-*N*-(benzoxycarbonyl)-3-oxo-3a,4,4a,5,6,7,8,9a-octanonahydrobenz[*f*]isoindole-4-carboxylate (6g) and Methyl (1*S*,3a*R*,4*S*,4a*S*,9a*R*)-1-(Acetoxymethyl)-2-*N*-(benzoxycarbonyl)-3-oxo-3a,4,4a,5,6,7,8,9a-octahydrobenz[*f*]isoindole-4-carboxylate (7g). A solution of diene **3a** (500 mg, 1.456 mmol) and maleic anhydride (428 mg, 4.368 mg) was refluxed in 1,2-dichlorobenzene (50 mL) as for **7a**. The crude acidic extracts (826 mg) were dissolved in ether (50 mL) and cooled to −10 °C in a conical flask. To this stirred solution was slowly added an ethereal solution of CH_2N_2 until the yellow color just persisted. A few drops of AcOH were added to discolor the solution. The solvent was evaporated and the residue dissolved in a minimum amount of MeOH and filtered through a 3 cm thick pad of reversed-phase silica using MeOH (100 mL) as the eluting solvent. After the solvent was evaporated from the filtrate the residue was dissolved in a minimum amount of EtOAc and filtered through a 4 cm thick pad of H60 silica (Merck) using EtOAc (150 mL) as the eluting solvent. The solvent was evaporated from the filtrate to give a brown oil (491 mg, 74% with regard to diene **3a**). ^{1}H and ^{13}C NMR spectroscopic analysis of the oil revealed a ratio of 2.7:1.0 for **6g** and **7g**. An aliquot of the crude product was analyzed by HPLC. Two peaks were detected with retention times of t = 10.9 min (**7g**) and t = 12.1 min (**6g**) in a ratio of 1.0:2.7, respectively. The crude product was dissolved in a minimum amount of hot MeOH (2 mL), and the solution was allowed to stand at rt for 1 h. The mother liquors were removed and the remaining crystals washed with ice-cold MeOH (1 mL) and dried to yield 54 mg of **7g** (8% with respect to diene **3a**): mp 202−203 °C; $[\alpha]^{25}_D$ = 120° (*c* 1.37, $CDCl_3$); IR (Nujol) 1760, 1740 cm^{-1}; ^{1}H NMR δ 12.2 (bs, 1 H), 7.44−7.31 (m, 5 H), 5.31, 5.26 (AB, J = 12 Hz, 2 H, Bn), 5.21 (bs, 1 H, H9), 4.86 (dd, J = 4,10 Hz, 1 H, H10), 4.30 (ddd, J = 4, 7, 9 Hz, 1 H, H1), 4.19 (dd, J = 9, 10 Hz, 1 H, H10), 3.78 (s, 3 H, OCH_3), 3.46 (dd, J = 4, 8 Hz, 1 H, H3a), 3.12 (m, 1 H, H9a), 2.92 (dd, J = 4, 6 Hz, 1 H, H4), 2.46 (m, 1 H, H4a), 2.25 (m, 1 H, H8$_{eq}$), 2.05 (s, 3 H, C(O)CH$_3$), 2.0 (m, 2 H, H5$_{eq}$, H8$_{ax}$), 1.8 (m, 2 H, H6$_{eq}$, H7$_{eq}$), 1.4−1.1 (m, 3 H, H7$_{ax}$, H6$_{ax}$, H5$_{ax}$); ^{13}C NMR δ 173.6, 171.9, 170.3 (CO), 152.0 (NC(O)O), 147.6 (CH=*C*), 135.1 (quaternary ar), 128.6, 128.4, 128.4, 112.2 (C=*C*H), 68.5 (Bn), 61.4 (CH_2O), 57.2 (CHN), 51.9 (OCH_3), 41.3 (*C*HCO$_2$H), 41.2 (*C*HC(O)N), 38.8 (C=C*C*H), 37.4 (C=C*C*H$_2$), 34.3 (C=CH*C*H), 31.4, 29.4, 27.2, 20.8 (C(O)*C*H$_3$). Anal. Calcd for $C_{25}H_{29}NO_7$: C, 65.92; H, 6.42; N, 3.07. Found: C, 65.75; H, 6.42; N, 2.95.

Diastereomeric **6g** was obtained (21% with respect to diene **3a**) as a colorless oil by HPLC of the mother liquor: $[\alpha]^{25}_D$ = −45.2° (*c* 1.63, CH_2Cl_2); IR (neat) 1795,1745−1730, 1700 cm^{-1}; ^{1}H NMR δ 7.38−7.30 (m, 5 H), 5.29, 5.26 (AB, J = 12 Hz, 2 H, Bn), 5.19 (bs, 1 H, H9), 4.39 (dd, J = 5, 12 Hz, 1 H, H10), 4.21 (dd, J = 4, 12 Hz, 1 H, H10), 4.11 (m, 1 H, H1), 3.77 (s, 3 H, OCH_3), 3.69 (dd, J = 4, 8 Hz, 1 H, H3a), 2.89 (m, 1 H, H4,), 2.88 (m, 1 H, H9a), 2.44 (m, 1 H, H4a), 2.25 (m, 2 H, H8$_{eq}$, H5$_{eq}$), 2.05 (s, 3 H, C(O)CH$_3$), 1.97 (m, 1 H, H8$_{ax}$), 1.75 (m, 2 H, H6$_{eq}$, H7$_{eq}$), 1.4 (m, 1 H, H7$_{ax}$), 1.21 (m, 1 H, H6$_{ax}$), 1.05 (m, 1 H, H5$_{ax}$); ^{13}C NMR δ 173.1, 171.7, 170.4, 151.5, 146.4 (C8a), 135.2, 128.8, 128.5, 127.9 (Ar), 116.5 (C9), 68.2 (Bn), 63.8 (C10), 60.8 (C1), 51.7 (OCH_3), 42.1 (C4), 40.2 (C3a), 38.4 (C4a), 36.7 (C8), 36.0 (C9a), 31.5 (C7), 29.3 (C7), 27.1 (C6), 20.7 (C(O)-*C*H$_3$). Anal. Calcd for $C_{25}H_{29}NO_7$: C, 65.92; H, 6.42; N 3.07. Found: C, 65.68; H, 6.62; N, 2.98.

JO9609743