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SYNTHETIC STUDIES TOWARDS GELSEMINE, I
THE IMPORTANCE OF THE ANTIPERIPLANAR EFFECT IN THE HIGHLY REGIOSELECTIVE REDUCTION OF NON-SYMMETRICAL CIS-HEXAHYDROPHTHALIMIDES‡

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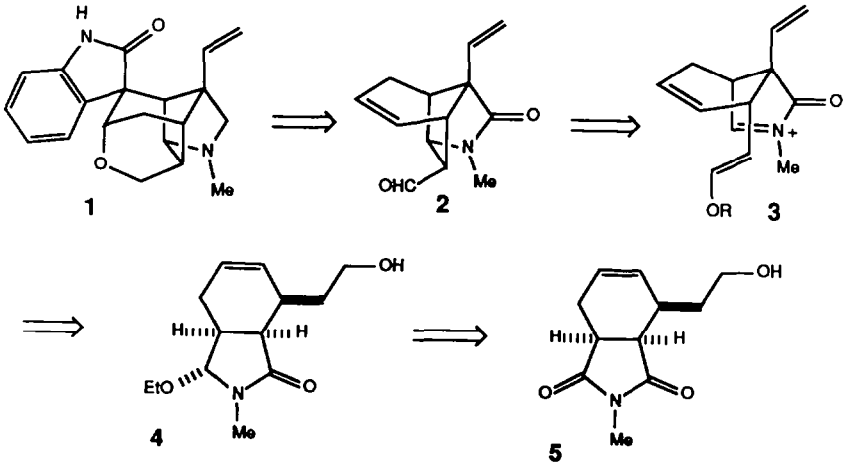
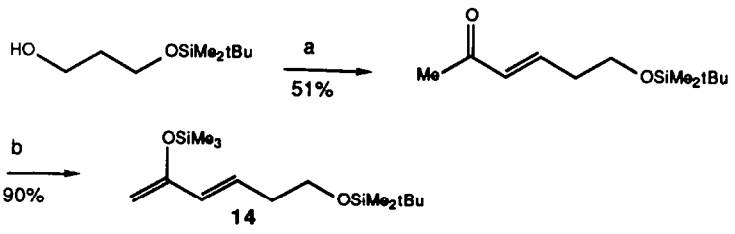
Abstract - During studies aimed at the total synthesis of gelsemine an exceptional example of regioselectivity has been discovered. cis-Hexahydrophthalimides, which are non-symmetrical through the presence of one alkyl group (see Figure 1), are reduced by sodium borohydride into the corresponding hydroxy lactams with very high regioselectivity. The corresponding cis-tetrahydrophthalimides exhibit much lower selectivity. These findings are explained on the basis of the conformational preference of the imide molecule and the antiperiplanar effect.

Gelsemine (1) is the principal alkaloid from Gelsemium sempervirens (Loganiaceae), a plant with a long medicinal history.[1] Although its unique molecular architecture was already established in 1959, gelsemine has not yet yielded to total synthesis despite some extensive efforts.[2] A few years ago we embarked upon a synthetic approach, which is based on the use of the ring closure of N-acyliminium intermediate 3 to tricycle 2 as the key step (Scheme I).[3] N-Acyliminium ion 3 is anticipated to arise from ethoxy lactam 4, which in turn should be available from tetrahydrophthalimide 5 through reduction and ethanolysis, respectively. It will be clear that the success of this synthetic endeavour highly depends on the regioselectivity of reduction of imide 5. In this paper we wish to report that reduction of 5 and structurally related imides can be highly regioselective. We present solid evidence that this synthetically important phenomenon is determined by the conformational preference of the imide molecule, and can be fully explained on the basis of the so-called antiperiplanar effect.



SCHEME I

‡ Dedicated to Professor Hans Wynberg of the University of Groningen on the occasion of his 65th birthday.

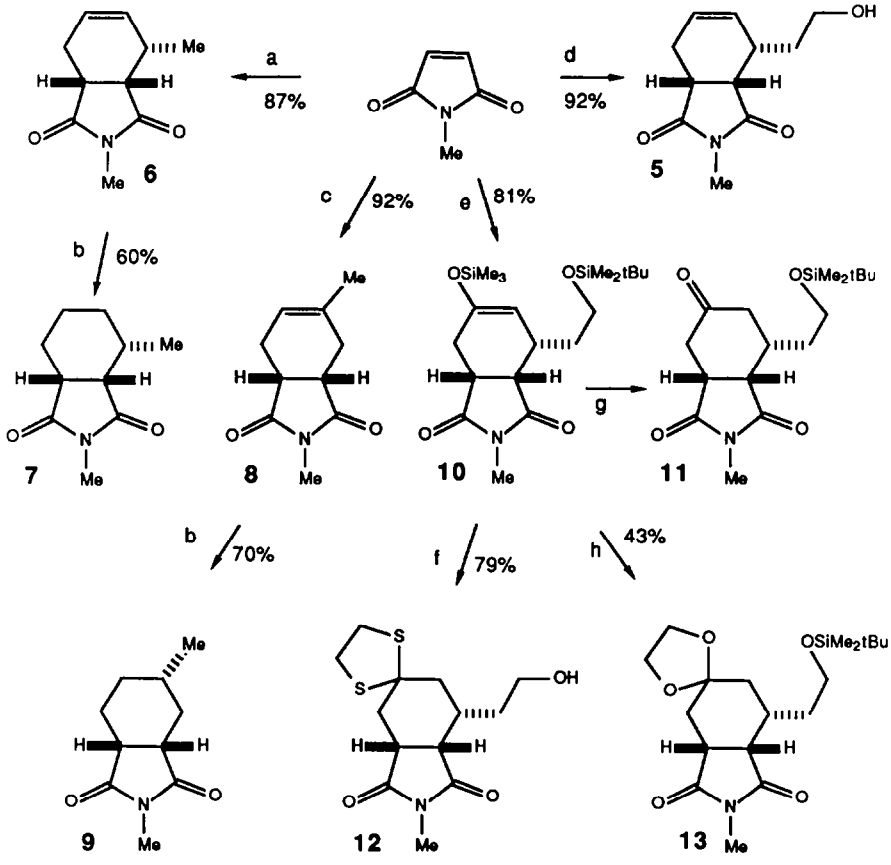


SCHEME III

a) 1. PCC, NaOAc, CH_2Cl_2; 2. $NEt(iPr)_2$, LiCl, MeCN, $MeCOCH_2PO(OMe)_2$.
b) Et_3N, Me_3SiOTf, Et_2O

Synthesis of the imides

The synthesis of the imides, which were subjected to reduction, are detailed in Scheme II. (Silyloxy)diene 14 was prepared as shown in Scheme III from mono-protected 1,3-propanediol[4] through, successively, oxidation to the aldehyde,[4] olefination[5] with 0,0-dimethyl(2-oxopropyl)phosphonate and silylation[6] with trimethylsilyl triflate. Diels-Alder reactions of commercially available N-methylmaleimide with trans-3,5-hexadien-1-ol[7], trans-piperylene, isoprene and (silyloxy)diene 14 provided high yields of isomerically pure adducts 5, 6, 8 and 10, respectively.[8] Hydrogenation of 6 and 8 furnished the saturated imides 7 and 9. One-pot dithioacetalization and hydrolysis of 10 afforded 12 in good yield.[9] Alternatively, acetalization with ethylene glycol provided 13.



SCHEME II

a) trans-1,3-pentadiene (3 eq), toluene, reflux, 19 h. b) hydrogen (1 atm), 10% Pd/C (cat), ethanol, 6 h. c) 2-methyl-1,3-butadiene (3 eq), toluene, reflux, 19 h. d) trans-3,5-hexadien-1-ol, toluene, reflux, 24 h. e) diene 14 (see Scheme III), triethylamine (0.05 eq), toluene, reflux, 3 h. f) 1,2-ethanedithiol (2.4 eq), boron trifluoride etherate (1.9 eq), dichloromethane, 0°C, 45 min. g) 0.0025N aq. sulfuric acid, THF, 80 min. h) ethylene glycol (10 eq), boron trifluoride etherate, dichloromethane, -5°C, 15 min.

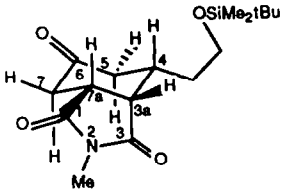
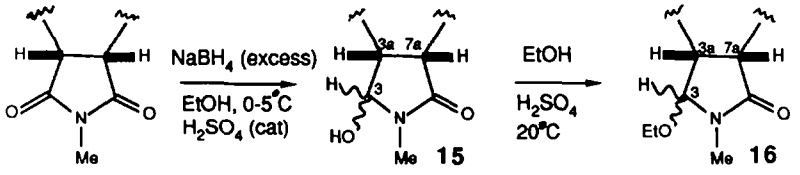


TABLE I. ^{1}H NMR data of imide 11 (250 MHz, $CDCl_3$)

H	δ (ppm)	coupling constants (Hz)
3a	3.22 (dd)	3a,7a= 9.5; 3a,4 = 5
4	~2.60 (m)	not resolved
5α	1.83 (dd)	5α,4 = 14; 5α, 5β = 19
5β	2.44 (dd)	5β,4 = 4 ; 5β, 5α = 19
7α	2.68 (dd)	7α,7β = 16.5; 7α,7a = 8
7β	2.87 (dd)	7β,7α = 16.5; 7β,7a = 2
7a	3.32 (ddd)	7a,7α = 8; 7a,7β = 2; 7a,3a = 9.5

There exists ample literature precedent[8] for the endo-selectivity of the Diels-Alder reaction, which in fact predicts the stereochemistry of 5, 7, 12 and 13. The 250 MHz ^{1}H NMR spectrum of ketone 11, which was obtained on mild hydrolysis of 10, provided additional evidence (Table I). The values of the vicinal coupling constants of the cyclohexanone hydrogen atoms point to a chair conformation with an equatorial [2-(silyloxy)]ethyl group (vide infra). These NMR data do not fit the exo-stereoisomer. The ^{13}C NMR spectrum of the hydrogenation product from 8 showed an about 5:1 mixture of stereoisomers, which were inseparable. It was later established (see the reduction of 9 in the Experimental) that the preponderant product was imide 9, resulting from addition of hydrogen to the (least-hindered) convex side of the bicyclic molecule.[10]



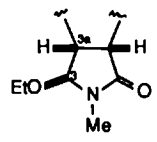
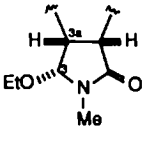
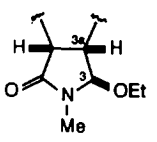
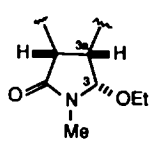
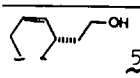
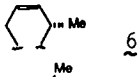
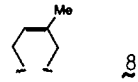
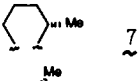
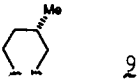
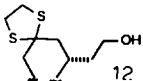
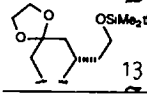
SCHEME IV

Reduction of the imides

The imides 5-9, 12 and 13 were reduced with excess $NaBH_4$ in ethanol (Scheme IV). Dilute sulfuric acid in ethanol was periodically added during the reduction to draw the reaction to completion (about 2 h).[11] The product mixture contained (at most) 4 isomeric hydroxy lactams 15, which (except in the case of 13, vide infra) were immediately ethanolyzed in the presence of excess sulfuric acid to the corresponding ethoxy lactams 16. The results are collected in Table II. Overall yields of ethoxy lactams were usually in 70-80% range. The remaining material mainly consisted of hydroxy lactams as a result of incomplete ethanolysis. In order to determine the regioselectivity of reduction, the product analysis was nevertheless performed on the ethoxy instead of the hydroxy lactams, despite the lower yield of the former, for reasons of convenience and accuracy, since ethoxy lactams are more stable and more suitable for chromatographic separation than hydroxy lactams. Although the non-quantitative yield of ethanolysis may slightly influence the regioselectivity data in the last column of Table II, the major trend is certainly not affected.

The assignment of the structures of the various ethoxy lactams was a demanding task. One of the questions was the relative orientation of H_3 and H_{3a}, being cis or trans in the γ-lactam ring. Molecular models indicated that the more favourable products should be those with H_3 and H_{3a} trans, having the ethoxy group at the convex side of the molecule. Since the ethanolysis reaction 15 → 16 (Scheme IV) is a thermodynamically controlled process, the trans-isomers were thus expected to be the major products. This expectation was borne out by the values of the ^{1}H NMR coupling constants between H_3 and H_{3a} shown in Table II. The major products exhibited a very small coupling and the minor products a coupling constant of about 5-6 Hz. From an examination of molecular models, assuming chair cyclohexane and boat cyclohexene conformations (vide infra), it was apparent that the dihedral angle $HC_3C_{3a}H$ is close to 90° in the trans- and smaller than 50° in the cis-isomers. MM2P calculations[12] on 25 and 26 in conformations as shown in Table III resulted in a $HC_3C_{3a}H$

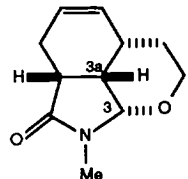
TABLE II. Results of the reduction ethanolysis sequence (Scheme IV)

imide	products				regio-selectivity of reduction
					
	no δ_3,ppm (% yield) ($J_{3,3a}$, Hz)	no δ_3,ppm (% yield) ($J_{3,3a}$,Hz)	no δ_3,ppm (% yield) ($J_{3,3a}$, Hz)	no δ_3, ppm (% yield) ($J_{3,3a}$, Hz)	left : right
 5	17(51) 4.32(1.5)	18(6) 4.65(6)	----	19(23)[a] 5.00(6)	73:27
 6	20(33) 4.33(2)	21(7) 4.63(6)	22(25) 4.47(2.8)	----	62:38
 8	23(37) 4.32(0)	24(3) 4.70(5.5)	23a(37) 4.32(0)	24a(3) 4.70(5.5)	50:50
 7	25(66) 4.16(0)	26(6) 4.59(5)	----	----	>95:5
 9	----	----	27 (53) 4.20(0)	28(5) 4.69(5.5)	<5:95
 12	29(77) 4.19(0)	----	----	----	>95:5
 13	30(40)[b] 4.12(0)	31(10)[b] 4.57(5.0)	----	----	>95:5

a) Not an ethoxy lactam, but a cyclic ether (see text).

b) Not an ethoxy, but a methoxy lactam, made via a basic method (see text).

angle of 79° in the trans- and 43° in the cis-isomer. Thus, according to Karplus' rule[13] the major products are the trans- and the minor the cis-isomers.[14] It is furthermore noteworthy that the chemical shift of H_3 is quite different in the trans- (~4.3 ppm) compared to the cis-series (~4.6 ppm). There is one exception to the rule that the major products have the trans arrangement of H_3 and H_{3a}, namely the formation of 19 from imide 5. However, 19 is not an ethoxy lactam but a cyclic ether, resulting from "intramolecular alcoholysis". Apparently, this cyclic ether is energetically favoured over the corresponding ethoxy lactam with a (2-hydroxy)-ethyl substituent.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The further structural assignment of the ethoxy lactam is based on a thorough analysis of the 250 MHz ^{1}H NMR spectra. With the aid of ^{1}H-shift correlated two dimensional NMR (COSY)[15] and double resonance experiments most of the signals in the spectra of the major products (17, 19, 20, 22, 23(a), 25, 27, 29 and 30 could be assigned. The structural assignment of the minor products is more tentative, since these could only rarely be obtained pure. The NMR spectral data are given in full detail in the Experimental. One aspect noted here is the similarity of the coupling patterns in the spectra 25, 29 and 30, which points to a chair cyclohexane ring with an equatorial C_7 substituent. The spectral data of 29 are given here (Table III) to illustrate this point.

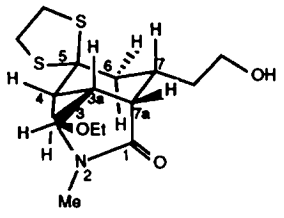
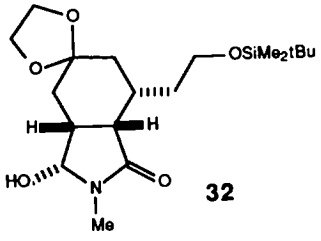


TABLE III. ^{1}H NMR data of ethoxy lactam 29 (250 MHz, $CDCl_3$)

H	δ(ppm)	coupling constants (Hz)
3	4.19 (s)	--
3a	2.49 (dt)	3a,7a = 6; 3a,4β = 6; 3a,4α = 12
4α	1.74 (dd)	4α,4β = 13; 4α,3a = 12
4β	~2.15	obscured
6α	1.55 (dd)	6α,6β = 13; 6α,7 = 12
6β	1.99 (dd)	6β,6α = 13; 6β,7 = 2
7	2.36 (m)	not resolved
7a	2.97 (t)	7a,3a = 6; 7a,7 = 6

The synthesis of 30 and 31 from imide 13 (Table II) needs a closer look. In the case of imide 13 the reduction product was not subjected to acidic ethanolysis, since such treatment would lead to the undesired loss of protecting groups. Instead, the reduction product mixture was worked up to afford hydroxy lactam 32 in 63% yield after chromatography. Other hydroxy lactams were not detectable in the ^{1}H NMR spectrum of the crude product. The orientation of the hydroxyl function was apparent from the magnitude of the vicinal coupling constant between H_3 and H_{3a}, amounting to 6.2 Hz. Treatment of 32 with NaH in THF, followed by excess methyl iodide furnished the mixture of methoxy lactams 30 and 31 (Table II). The isomerization must be a result of a fast base induced ring-chain tautomerization, before alkylation takes place.



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Rationalization of the regioselectivity of the imide reduction

The results with respect to the regioselectivity of reduction of the imides shown in Table II can be summarized as follows (see also Figure 1). Hexahydrophthalimides 7, 9, 12 and 13 give a very high regioselectivity, but dependent on the site of the α-disposed substituent (4α or 5α), either for the left- or the right-hand carbonyl group. The tetrahydrophthalimides exhibit a much lower regioselectivity of reduction, if the substituent occupies the 4-position (imides 5 and 6) and no selectivity at all if the substituent is on the double bond (imide 8). At first glance, the two carbonyl groups in all of these imides do not look very different. Clearly, the presence of a hydroxyl group in the side-chain is unimportant in determining the regioselectivity. How then could one rationalize these striking results ?

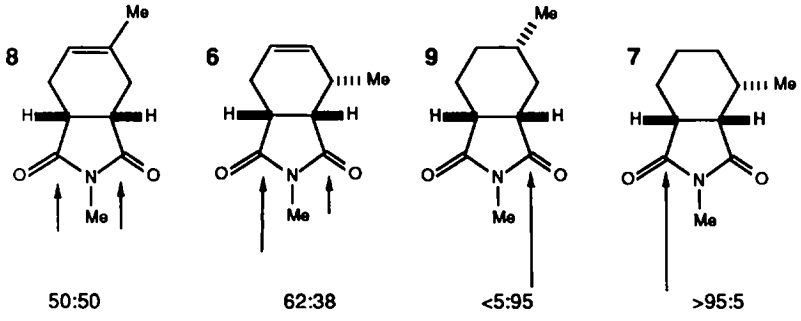


Figure 1. Regioselectivity of reduction of methyl substituted imides 6 - 9

About one decade ago, an extensive study was published on the regioselectivity of the reduction of 3-mono- and 3,3-disubstituted succinimides.[14] It appeared that in case of the 3,3-disubstituted succinimides a high preference is found for reduction at C_2, the more sterically encumbered carbonyl group. 3-Monosubstituted succinimides exhibited only low regioselectivity. Comparable results had been found earlier in reductions of similarly substituted succinic anhydrides.[16,17]

Various other more complex molecules containing the succinic anhydride moiety have also displayed highly regioselective behaviour with respect to carbonyl reduction.[18,19] A recent report on regioselective addition of acetylide anions to non-symmetrical 1,4,4a,5,8,8a-hexahydronaphthalene-1,4-diones[20] bears resemblance to the imide and anhydride reduction reaction.

In an attempt to explain the regioselectivity of the carbonyl addition process, Dunitz and coworkers proposed the theory of the non-perpendicular, restricted path of nucleophilic approach. According to this theory the substituent at C_3 in 3,3-disubstituted succinimides (or succinic anhydrides) hinder the approach to carbonyl C_5 more than they hinder the approach to carbonyl C_2.[15,21] However, this theory fails to explain the observed regioselectivity in a considerable number of cases.[20,22] After a comprehensive study Kayser and coworkers concluded that the observed regioselectivity is the net result of the interplay between three effects, namely a) the conformation of the molecule and the steric contraints associated with it, b) the intrinsic reactivities of the two carbonyl functions, and c) the possibility of antiperiplanar attack.[19,22] These three factors sufficed to account for the regioselectivities observed for non-symmetrical anhydrides. Do one or more of these effects provide an explanation also for the imides (Table II) of this study ?

To begin with effect b, the intrinsic reactivities of the two carbonyl functions are equal, since in all imides studied here the carbon atoms C_{3a} and C_{7a} and in some cases (8, 9) even the carbons C_4 and C_7 have identical substitution patterns. The electronic similarity of the two carbonyl groups is confirmed by ^{13}C NMR spectroscopy, which shows less then 2 ppm difference in chemical shift between C_1 and C_3 in imides 5-9. It should be noted that the tetra- and hexahydrophthalic anhydrides studied by Kayser et al. have already an unequal substitution pattern at C_{3a} and C_{7a},[17,19] so our imides pose a different problem. Do then the conformations of the imides

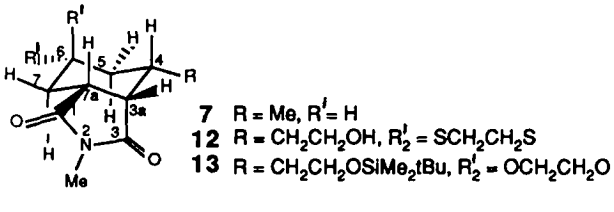
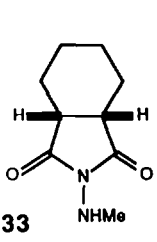


Figure 2. Preferred conformations of imides 7, 9, 12, and 13.

reveal a reactivity difference between the carbonyl groups ? The hexahydrophthalimides are considered first. The ^1H NMR coupling constants of imide 11 (Table I) point to a chair cyclohexanone ring. A comprehensive ^1H NMR study has shown that methyl substituted cis-hexahydrophthalic anhydrides contain a chair-cyclohexane ring with an equatorial methyl group.[23] It is, therefore, reasonable to assume that the imides 7, 9, 12 and 13 adopt as their preferred conformation a chair cyclohexane ring with the least number of axial substituents. These conformations are depicted in Figure 2. Further evidence for these conformations comes from X-ray crystallographic data of related molecules, available from the literature. Imide 33[24] and anhydrides 34[25] and 35[26] appear to have chair cyclohexane rings, and this is particularly interesting in the case of 35 which has an axial methoxy group. (Due to their very similar geometry succinimides and succinic anhydrides can be compared without hesitation). Assuming now, that the preferred conformation is the reactive one, the crucial issue is the difference between the two carbonyl groups: The one carbonyl group occupies an equatorial position and the other an axial position. The results in Table II show that there is an enormous preference for reduction of the equatorially disposed carbonyl group in all hexahydrophthalimides studied. It is rather hard to imagine that simple steric reasons can account for this large reactivity difference between an axial and equatorial carbonyl group, since they both seem well exposed to nucleophilic attack from the convex side. Therefore, we propose that the reactivity difference is a result of the antiperiplanar effect, the third factor cited by Kayser et al.[19,22]



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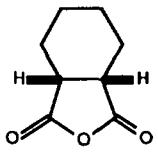

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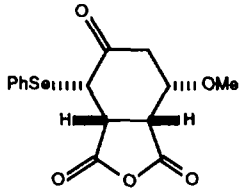

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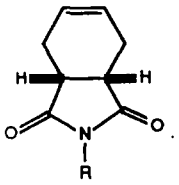


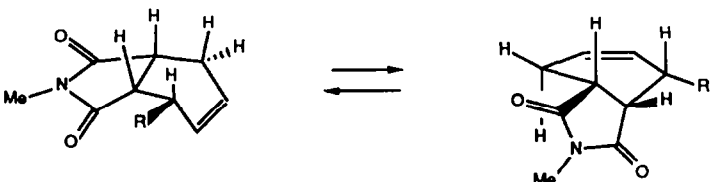
36 R = H
37 R = $SCCl_3$

The antiperiplanar effect[27] for nucleophilic addition to a carbonyl group states, that such a reaction proceeds best, if the adjacent sp^3 carbon has one (preferably the most electronegative) substituent disposed perpendicularly with respect to the plane of the carbonyl group. The nucleophile then approaches the carbonyl group antiperiplanar with respect to this perpendicular substituent. Several recent publications provide both theoretical and experimental evidence for the antiperiplanar effect.[28]

Since crystallographic data on our hexahydrophthalimides were not available, we performed MM2P calculations[12] in order to acquire exact information on the geometry of the molecules. These studies clearly showed that the chair cyclohexane ring forces the five-membered imide ring into a half-chair conformation. In the half-chair imide ring of e.g. 7 (Figure 2) the $C_{7a}C_7$ bond and the $C_{3a}H$ bond occupy quasi-axial positions. Stated otherwise, the $C_{7a}C_7$ bond is nearly perpendicular with respect to the plane of the equatorial carbonyl group C_1 (the average plane through C_{7a}, C_1, O_1 and N) and the same is true for the $C_{3a}H$ bond with respect to the plane of the axial carbonyl C_3. Thus, antiperiplanar attack means for C_1 approach, from the convex side and for C_3 approach, from the concave side of the molecule. The latter reaction is clearly sterically hindered by two axial hydrogen atoms at C_5 and C_7, thus the equatorial carbonyl group is the most reactive. That hydride indeed attacks C_1 from the convex side has been proved in the case of reduction of imide 13, which afforded hydroxy lactam 32 as the single product. In conclusion, a combination of the antiperiplanar effect and steric factors explains the regioselectivity of reduction of hexahydrophthalimides 7, 9, 12 and 13.

Let us then consider the tetrahydrophthalimides 5, 6 and 8. It is very probable that these compounds have a boat cyclohexene ring. X-ray crystallographic data are available on imides 36[29] and 37[30], which both have their cyclohexene rings in a boat conformation. ^{1}H NMR coupling constants of corresponding anhydrides[26,31–33] also point to boat-like cyclohexene rings in these molecules. Unfortunately, the ^{1}H NMR spectra of 5, 6 and 8 did not give conclusive information.

Conformational options for imide 6 are shown in Figure 3. If 6 were to react in a conformation with a boat cyclohexene ring, very little regioselectivity would be expected since the geometry around both carbonyl groups is similar. On the other hand, a conformation with a half-chair cyclohexene ring has an equatorial and an axial carbonyl group and thus a similar reasoning as in the case of the saturated imides is possible. The rather low selectivities obtained with 5 and 6 render further conclusions inappropriate. The zero selectivity reached with 8 is in accord with expectation, since in this case both possible half-chair conformations are of nearly equal stability.



5 R = CH_2CH_2OH
6 R = Me

Figure 3. Possible conformations for imides 5 and 6.

Conclusion

We have described an exceptional example of regioselectivity in organic chemistry, which is determined by the high preference of a cyclohexane ring to occur in a chair conformation with the least number of axial substituents. As a consequence, a cis-fused succinimide moiety is forced to adopt a half-chair conformation, in which one carbonyl group is equatorial and the other axial with respect to the cyclohexane ring. The equatorial carbonyl group is much more susceptible to nucleophilic (hydride) attack than the axial one. This reactivity difference is caused by the anti-periplanar effect and steric factors associated with it. Since the preference for one specific conformation is less pronounced for cyclohexenes, lower regioselectivity is observed in cis-fused succinimide derivatives thereof.

EXPERIMENTAL

General Procedures. Infrared spectra (IR) were obtained from $CHCl_3$ solutions on a Perkin Elmer 298 or 1310 spectrophotometer and are reported in cm^{-1}. Proton (^1H) and ^{13}C nuclear magnetic resonance (NMR) spectra were determined in $CDCl_3$ solutions (unless otherwise indicated) on a Varian XL-100, Bruker AC-200 or Bruker WM-250 instrument. Chemical shifts are given in ppm downfield from tetramethylsilane. Signals were assigned with the aid of double resonance, COSY[35] (^1H NMR) and APT[36] (^{13}C NMR). Accurate mass measurements were performed on a Varian MAT 711 instrument. R_f values were obtained via thin layer chromatography (TLC) on silica gel coated plastic sheets[1] (Merck silica 60 F_{254}) with the indicated solvent (mixture). Chromatographic purification refers to flash chromatography[35] using the same solvent as for TLC (unless otherwise indicated) and Merck silica gel 60 (230-400 mesh).

3-[tert-Butyldimethylsilyl)oxy]-propanal.[4] To a mixture of 261 mg (1.37 mmol) of 3[(tert-butyl-dimethylsilyl)oxy]-1-propanol and 90 mg (1.10 mmol) of dry sodium acetate in 5.4 ml of dichloro-methane was added at 0°C all at once 570 mg (2.64 mmol) of pyridinium chlorochromate. TLC analysis showed that the reaction was complete after 2.5 h of stirring at room temperature. The mixture was then diluted with 20 ml of ether, stirred vigorously for 15 min, and filtered over a 1:1 mixture of silica gel (Woelm, 100-200 mesh) and Florisil (60-100 mesh). The solid residue was stirred with 20 ml of ether and filtered in the same manner. This procedure was repeated one more time. The combined filtrates were washed with 2N aqueous NaOH (30 ml) and brine (40 ml), dried ($MgSO_4$) and concentrated in vacuo (10 mm Hg) to give 220 mg (1.17 mmol, 85%) of an orange-yellow oil: R_f 0.37 (EtOAc/hexane 1:6); ^1H NMR (100 MHz): δ9.78 (t, J=2 Hz, 1H), 3.93 (t, J=6 Hz, 2H), 2.53 (dt, J=6, 2 Hz, 2H), 0.82 (s, 9H), 0.00 (s, 6H). This crude aldehyde was immediately used in the following preparation.

6-[(tert-Butyldimethylsilyl)oxy]-3-hexen-2-one.[5] To a stirred solution of 765 mg (18 mmol) of lithium chloride (dried in vacuo at 150°C overnight; weighed under nitrogen atmosphere) in 100 ml of acetonitrile (freshly distilled from CaH_2) was added dropwise at room temperature under nitrogen a solution of 2.49 g (15 mmol) of dimethyl-(2-oxopropyl)-phosphonate in 12 ml of acetonitrile. After 15 min 3.14 ml of diisopropylethylamine (2.33 g, 18 mmol) was added dropwise. The reaction mixture changed to a clear yellow solution. After 2 h 3.14 g of crude aldehyde (see preceding procedure, 16.7 mmol) in 20 ml of acetonitrile was added over 10 min. The resulting mixture was stirred overnight and then diluted with 25 ml of water and 50 ml of brine. The organic layer was separated and the aqueous layer extracted twice with 75 ml of ether. The combined organic solutions were washed with brine (2x50 ml), dried ($MgSO_4$) and concentrated in vacuo. The residue (4.2 g) was chromatographed to afford 2.34 g (10.2 mmol, 51% from mono-protected 1,3-propanediol) of a colourless oil: R_f 0.36 (EtOAc/hexane 1:4); IR 1672, 1630, 1255, 980, 840; ^1H NMR (100 MHz) δ6.78 (dt, J=16, 7 Hz, 1H), 6.05 (dt, J=16, 1 Hz, 1H), 3.69 (t, J=7 Hz, 2H), 2.33 (ddt, J=7, 6, 1 Hz, 2H), 2.18 (s, 3H), 0.83 (s, 9H), -0.01 (s, 6H).

4α-{2-[(tert-Butyldimethylsilyl)oxy]ethyl-2-methyl-6-[(trimethylsilyl)oxy]-3aβ,4,7,7aβ-tetra-hydro-1H-isoindole-1,3(2H)-dione (10). To a solution of the above enone (1.58 g, 6.92 mmol) in 35 ml of dry ether were added under nitrogen at room temperature, successively, 1.16 ml (8.3 mmol) of triethylamine and dropwise 1.47 ml (7.6 mmol) of trimethylsilyl triflate. The resulting mixture was stirred for 40 min at room temperature, and then diluted with 35 ml of 1N aqueous $NaHCO_3$ and 70 ml of ether/hexane 1:1. The aqueous layer was once more extracted with 130 ml of ether/hexane 1:1. The combined organic solutions were washed with 50 ml of 1N aqueous $NaHCO_3$, dried (K_2CO_3) and concentrated in vacuo to afford 2.08 g (6.92 mmol, 100%) of light yellow oil, which was used as such in the Diels Alder reaction: R_f 0.58 (EtOAc/hexane 1:6); ^1H NMR (100 MHz) δ6.06-5.77 (m, J=15 Hz, 2H), 4.20 (s, 2H), 3.62 (t, J=7 Hz, 2H), 2.45-2.15 (m, 2H), 0.86 (s, 9H), 0.18 (s, 9H), 0.01 (s, 6H).

A mixture of this crude diene, 0.05 ml (0.36 mmol) of triethylamine, 0.789 g (7.1 mmol) of N-methylmaleimide and 20 ml of dry toluene was refluxed for 3 h under nitrogen. It was then cooled to room temperature and mixed with 20 ml of water and 10 ml of brine. The organic layer was separated and the aqueous layer extracted with $CHCl_3$ (3x25 ml) and dichloromethane (3x10 ml). The combined organic solutions were dried ($MgSO_4$) and concentrated in vacuo to afford 3.03 g of a yellow oil. Chromatographic purification furnished 2.32 g (5.64 mmol, 81%) of 10 as a yellow oil: R_f 0.11 (EtOAc/hexane 1:4); IR 3030, 1770, 1705, 1640, 1250, 840; ^1H NMR (100 MHz) δ4.63 (m, 1H), 3.58-3.84 (m, 2H), 2.84-3.17 (m, 2H), 2.87 (s, 3H), 1.58-2.60 (m, 5H), 0.83 (s, 9H), 0.07 (s, 9H), -0.01 (s, 6H). Further elution with EtOAc/hexane 2:3 provided 230 mg (0.68 mmol, 10%) of reasonably pure ketone 11, which crystallized from EtOAc: mp 44-46.5°C; R_f 0.33 (EtOAc/hexane 1:1); IR 1775, 1705, 1250, 835; ^1H NMR (250 MHz): see Table I for cyclohexane ring hydrogens, 3.77 (m, CH_2OSi), 2.96 (s, NCH_3), 2.07 (m, 1H), 1.71 (m, 1H), 0.86 (s, $C(CH_3)_3$), 0.03 (s,

$Si(CH_3)_2$; ^{13}C NMR (63 MHz) δ207.5 (C_1), 178.2 and 177.0 (C_1, C_3), 60.1 (CH_2OSi), 42.2 (C_5 or C_7), 41.0 and 38.1 (C_{3a}, C_{7a}), 37.2 (C_5 or C_7), 34.1 ($\underline{CH_2}CH_2OSi$), 30.7 (C_4), 25.8 (q, $C(CH_3)_3$, 24.8 (NCH_3), 18.1 (SiC), -5.5 and -5.6 ($Si(CH_3)_2$); exact mass calcd for $C_{13}H_{20}NO_4Si$ (= $M^+-C(CH_3)_3$) 282.1162, found 282.1162.

6,6-Ethylenedithio-4α-[(2-hydroxy)ethyl]-2-methyl-3aβ,4,5,6,7,7aβ-hexahydro-1H-isoindole-1,3(2H)-dione (12). A mixture of 10 and 11 (1.05 g, 2.55 mmol, ratio 3:1) was dissolved in 5 ml of dichloromethane. The resulting solution was cooled to 0°C and then treated with 0.50 ml (6.0 mmol) of 1,2-ethanedithiol followed by 0.60 ml (4.85 mmol) of boron trifluoride etherate. The reaction mixture was allowed to stir for 45 min at room temperature and was then poured into 30 ml of saturated aqueous $NaHCO_3$. Extraction with chloroform (3x25 ml) gave an organic solution, which was washed with brine (20 ml), dried (K_2CO_3) and concentrated in vacuo. Chromatography of the residue furnished 604 mg (2.01 mmol, 79%) of a white solid: mp 111-116°C; R_f 0.31 (EtOAc); IR 3600, 3450, 1770, 1700; ^1H NMR (250 MHz) δ3.79 (m, CH_2OSi), 3.28 (m, CH_2S), 3.03-3.14 (m, H_{3a}, H_{7a}), 2.91 (s, NCH_3), 2.54 (m, $H_{7\beta}$), 2.15-2.38 (m, H_4, $\underline{CH}HCH_2OSi$), 2.13 (m, $H_{5\beta}$), 1.68-1.90 (m, OH, $H_{7\alpha}$, $H_{5\alpha}$, $CH\underline{HCH_2}OSi$).

4α-{2-[(tert-Butyldimethylsilyl)oxy]}ethyl-6,6-ethylenedioxo-2-methyl-3aβ,4,5,6,7,7aβ-hexahydro-1H-isoindole-1,3(2H)-dione (13). To a mixture of 1.4 g (3.4 mmol) of 10 and 1.96 g (32 mmol) of 1,2-ethanediol in 7 ml of dichloromethane, cooled at -6°C, was added dropwise under nitrogen 1.68 ml (13.6 mmol) of boron trifluoride etherate. The resulting mixture was stirred at -5°C for 15 min and then diluted with 10 ml of 1N aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer extracted with chloroform (3x25 ml). The combined organic solutions were washed with brine (20 ml), dried (K_2CO_3) and concentrated in vacuo to give 1.44 g of yellow oil. Chromatographic separation of the products gave 555 mg (1.45 mmol), 43%) of desired 13 as a light yellow oil: R_f 0.38 (EtOAc/hexane 1:1); IR 1775, 1700, 1255, 1140, 840; ^1H NMR (250 MHz) δ3.63-3.91 (m, OCH_2), 2.83-3.02 (m, H_{3a}, H_{7a}), 2.92 (s, NCH_3), 2.27 (m, H_4), 1.74-2.17 (m, 5H), 1.46 (dd, J=14, 15 Hz, $H_{5\alpha}$), 0.87 (s, $C(CH_3)_3$), 0.03 (s, $Si(CH_3)_2$); exact mass calcd for $C_{15}H_{24}NO_5Si$ (=M-tert-butyl) 326.1475, found 326.1419.

4α-[(2-Hydroxy)ethyl]-2-methyl-3aβ,4,7,7aβ-tetrahydro-1H-isoindole-1,3(2H)-dione (5). A solution of 6.59 g (67 mmol) of trans-3,5-hexadien-1-ol and 7.45 g N-methylmaleimide (67 mmol) in 55 ml of dry toluene was refluxed for 24 h under nitrogen. The toluene was removed in vacuo and the residue chromatographed to furnish 12.95 g (62 mmol, 92%) of a colourless oil, which crystallized from EtOAc: mp 61-64°C; R_f 0.25 (EtOAc); IR 3450, 3050-2840, 1770, 1690; ^1H NMR (250 MHz) δ5.87 (m, H_6), 5.70 (m, H_5), 3.71-3.96 (m, CH_2OH), 3.27 (dd, J=6.6, 8.7 Hz, H_{3a}), 3.11 (ddd, J=8.7, 7.2, 1.5 Hz, H_{7a}), 2.90 (s, Me), 2.71 (ddd, J=15.2, 6.9, 1.5 Hz, $H_{7\alpha}$), 2.49 (m, H_4), 2.09-2.28 (m, $H_{7\beta}$ and $CHHCH_2OH$), 2.07 (br s, OH), 2.00 (m, $CHHCH_2OH$), assignments follow from COSY and decoupling; ^{13}C NMR (50 MHz): δ179.8 and 178.4 (C_1, C_3), 133.5 (C_5), 127.4 (C_6), 60.6 (OCH_2), 42.5 and 40.1 (C_{3a}, C_{7a}), 33.6 ($\underline{CH_2}CH_2O$), 32.5 (C_4), 24.4 (NCH_3), 23.9 (C_7); exact mass calcd for $C_{11}H_{13}NO_2$ (= M^+-H_2O) 191.0946, found 191.0945.

2,4α-Dimethyl-3aβ,4,7,7aβ-tetrahydro-1H-isoindole-1,3(2H)-dione[36] (6). A solution of 13 ml (8.9 g, 130 mmol) of trans-piperylene and 4.7 g (42.3 mmol) of N-methylmaleimide in 44 ml of dry toluene was refluxed for 19 h. The volatiles were removed in vacuo and the residue chromatographed to furnish 6.59 g (36.8 mmol, 87%) of a colourless oil: R_f 0.32 (EtOAc/hexane 3:2); IR 1770, 1700; ^1H NMR (250 MHz) δ5.76 (m, H_6), 5.65 (m, H_5), 2.88-3.07 (m, H_{3a}, H_{7a}), 2.83 (s, NCH_3), 2.59 and 2.40 (m, $H_{7\alpha}$, $H_{7\beta}$), 2.08 (m, H_4), 1.28 (d, J=7 Hz, CH_3); ^{13}C NMR (50 MHz) δ179.9 and 178.0 (C_1, C_3), 134.7 (C_5), 126.8 (C_6), 44.2 and 40.1 (C_{3a}, C_{7a}), 30.2 (C_4), 24.4 (NCH_3), 23.6 (C_7), 16.5 (CH_3); exact mass calcd for $C_{10}H_{13}NO_2$ 179.0946, found 179.0947.

2,4α-Dimethyl-3aβ,4,5,6,7,7aβ-hexahydro-1H-isoindole-1,3(2H)-dione (7). A solution of olefin 6 (2.0 g, 11.2 mmol) in 130 ml of ethanol was shaken under an atmosphere of hydrogen for 6 h in the presence of 150 mg of 10% palladium on carbon catalyst. The catalyst was removed through filtration over celite and the filtrate concentrated in vacuo. The residue was chromatographed to furnish 1.20 g (6.6 mmol, 59%) of a colourless oil: R_f 0.30 (EtOAc/hexane 1:2); IR 1770, 1695; ^1H NMR (200 MHz) δ2.94 (s, NCH_3), 2.85-2.91 (m, H_{3a}, H_{7a}), 1.82-2.04 (m, 2H), 1.41-1.72 (m, 4H), 1.21 (d, J=7 Hz, CH_3), 1.09-1.24 (m, 1H); ^{13}C NMR (50 MHz) δ180.2 and 178.5 (C_1, C_3), 44.3 and 40.7 (C_{3a}, C_{7a}), 28.9 (C_4), 27.9 (C_5), 24.2 (NCH_3), 23.0 and 19.3 (C_6, C_7), 18.3 (CH_3); exact mass calcd for $C_{10}H_{15}NO_2$ 181.1103, found 181.1105.

2,5-Dimethyl-3aβ,4,7,7aβ-tetrahydro-1H-isoindole-1,3(2H)-dione[37] (8). A solution of 9.6 g (14 ml, 140 mmol) of isoprene and 5.0 g (45 mmol) of N-methylmaleimide in 45 ml of toluene was refluxed for 19 h. The volatiles were removed in vacuo and the residue chromatographed to furnish 7.44 g (41.5 mmol, 92%) of a colourless oil: R_f 0.31 (EtOAc/hexane 1:1); IR 1775, 1695; ^1H NMR (200 MHz) δ5.45 (m, H_6), 2.92-3.08 (m, H_{3a}, H_{7a}), 2.87 (s, NCH_3), 2.47 (m, 1H) 2.40 (m, 1H), 2.05-2.19 (m, 2H), 1.64 (br s, CH_3); ^{13}C NMR (50 MHz) δ180.2 and 179.9 (C_1, C_3), 136.1 (C_5), 119.9 (C_6), 39.3 and 38.8 (C_{3a}, C_{7a}), 28.4 (C_4), 24.7 (NCH_3), 23.9 (C_7), 23.2 (CH_3); exact mass calcd for $C_{10}H_{13}NO_2$ 179.0946, found 179.0949.

2,5α-Dimethyl-3aβ,4,5,6,7,7aβ-hexahydro-1H-isoindole-1,3(2H)-dione (9). A solution of olefin 8 (2.4 g, 13 mmol) in 130 ml of ethanol was shaken under an atmosphere of hydrogen for 6 h in the presence of 150 mg of 10% palladium on carbon catalyst. The catalyst was removed through filtration over celite and the filtrate concentrated in vacuo. The residue was chromatographed to furnish 1.67 g (9.2 mmol, 71%) of an oil: R_f 0.30 (EtOAc/hexane 1:2); IR 1770, 1695; ^1H NMR (200 MHz) δ2.92 (s, NCH_3), 2.79-2.86 (m, H_{3a}, H_{7a}), 2.23 (m, 1H), 2.10 (m, 1H), 1.74-1.52 (m, 2H), 1.50-0.75 (m, 3H), 0.86 (s, J=6.5 Hz, CH_3); ^{13}C NMR (50 MHz) showed the presence of two isomers in a ratio of about 5:1; data of major isomer: δ180.1 and 179.1 (C_1, C_3), 40.3 and 39.3 (C_{3a}, C_{7a}), 34.9 (C_4), 30.5 and 21.3 (C_6, C_7), 29.0 (C_5), 24.5 (NCH_3), 22.1 (CH_3); exact mass calcd for $C_{10}H_{15}NO_2$ 181.1103, found 181.1099.

General procedure for the one-pot reduction-ethanolysis process (Scheme IV). To a stirred solution of the imide (10.6 mmol) in 90 ml of ethanol was added at 0°C all at once 2.8 g (74.2 mmol) of

$NaBH_4$. The mixture was stirred at 0-5°C, while 6 drops of a 2M solution of H_2SO_4 in ethanol were added every 15 min. The reaction was monitored by TLC and was complete in most cases after 2 h (total amount of 2M H_2SO_4 in ethanol added was about 4 ml). The reaction mixture was then treated at 0°C with a 6M H_2SO_4 solution in ethanol until a pH of about 1-2 was reached. The resulting mixture was stirred overnight at room temperature. The mixture was then slowly poured out into a well stirred saturated aqueous $NaHCO_3$ solution (200 ml). Extraction with chloroform (4x100 ml) gave an organic solution which was washed with brine (100 ml), dried (K_2CO_3) and concentrated in vacuo to afford the crude mixture of ethoxy lactams.

Reduction of imide 5. From 6.0 g (28.7 mmol) of 5 was obtained 7.07 g of crude product after a reduction period of 3.5 h and an ethanolysis period of 17 h. Separation of the various products required tedious chromatography, but finally led to the isolation of 3 reasonably pure compounds (see Table II), namely 17 (3.49 g, 14.6 mmol, 51%), 18 (0.38 g, 1.59 mmol, 6%) and cyclic ether 19 (1.3 g, 6.73 mmol, 23%). Data for these products: 3β-Ethoxy-7α-[(2-hydroxy)ethyl]-2-methyl-2,3,3aβ,4,7,7aβ-hexahydro-1H-isoindol-1-one (17): R_f 0.18 (EtOAc); IR 3400, 1675; ^{1}H NMR (250 MHz) δ5.64-5.80 (m, H_5, H_6), 4.32 (d, J=1.5 Hz, H_3), 3.63-3.86 (m, CH_2OH), 3.45 (q, J=7 Hz, OCH_2CH_3), 3.17 (br, OH), 3.09 (dd, J=6, 8.5 Hz, H_{7a}), 2.74 (s, NCH_3), 2.56 (m, H_{3a}), 1.84-2.42 (m, 5H), 1.18 (t, J=7 Hz, CH_3CH_2O) signals assigned with the aid of decoupling; ^{13}C NMR (50 MHz) δ175.9 (C_1), 134.7 (C_6), 126.3 (C_5), 97.0 (C_3), 62.0 (CH_2O), 61.5 (CH_2O), 42.9 and 37.6 (C_{3a}, C_{7a}), 33.4 (C_7), 33.7 (CCH_2OH), 27.4 (NCH_3), 26.6 (C_4), 15.3 (CCH_3); exact mass calcd for $C_{13}H_{21}NO_3$ 239.1521, found 239.1530. Isomer 18: R_f 0.13 (EtOAc); ^{1}H NMR (100 MHz) δ5.64-5.96 (m, H_5, H_6), 4.65 (d, J=6 Hz, H_3), 3.40-3.88 (m, CH_2OH), 3.62 (q, J=7 Hz, OCH_2CH_3), 2.78 (s, NCH_3), 1.55-2.95 (m, 7H), 1.20 (t, J=7 Hz, OCH_2CH_3). Cyclic ether 19: R_f 0.23 (EtOAc); IR 1680; ^{1}H NMR (250 MHz) δ5.92 (m, H_6), 5.68 (m, H_5), 5.00 (d, J=6 Hz, H_3), 3.60 (m, OCH_2), 2.76 (s, NCH_3), 2.66-2.76 (m, H_{3a}, H_{7a}), 2.57 (m, H_7), 2.44 (m, H_4), 2.09 (m, H_7), 1.53-1.97 (m, CH_2CH_2O); ^{1}H NMR (250 MHz, C_6D_6) δ5.82 (m, H_6), 5.41 (m, H_5), 4.43 (d, J=6 Hz, H_3), 3.23 (m, OCH_2), 2.69 (m, H_7), 2.62 (s, NCH_3), 2.26 (m, H_{7a}), 1.76-2.02 (m, H_{3a}, H_4, H_7), 1.41 (m, $CHHCH_2O$), 1.07 (m, $CHHCH_2O$); ^{13}C NMR (50 MHz) δ175.8 (C_1), 132.5 (C_5), 128.4 (C_6), 86.3 (C_3), 58.2 (OCH_2), 40.7 and 33.0 (C_{3a}, C_{7a}), 28.1 (CH_2CH_2O), 26.9 (CH_3), 26.8 (C_4), 23.2 (C_7); exact mass calcd for $C_{11}H_{15}NO_2$ 193.1103, found 193.1096.

Reduction of imide 6. From 1.0 g (5.60 mmol) of 6 were obtained after a reduction period of 2 h, an ethanolysis period of 48 h and tedious chromatographic separation pure samples of 20 (143 mg) and 22 (57 mg). Isomer 21 could not be completely separated from 20 and 22. The product ratio given in Table II was determined by integration of the signals for H_3 in the ^{1}H NMR spectrum of the crude product (762 mg, 65%). Data for 20 and 22: 2,7α-Dimethyl-3β-ethoxy-2,3,3aβ,4,7,7aβ-hexahydro-1H-isoindol-1-one (20): R_f 0.45 (EtOAc/hexane 3:1); IR 1680; ^{1}H NMR (250 MHz) δ5.67 (m, H_6, H_7), 4.33 (d, J=2.1 Hz, H_3), 3.45 (q, J=7 Hz, OCH_2), 2.76 (m, H_{7a}), 2.72 (s, NCH_3), 2.47 (m, H_{3a}), 2.36 (m, H_7), 2.15 (dd, J=16, 8 Hz, H_4), 2.00 (dt, J=16, 4.5 Hz, H_4), 1.12-1.25 (d, t, J=7 Hz, 2xCH_3); ^{13}C NMR (50 MHz) δ175.3 (C_1), 134.7 (C_6), 125.1 (C_5), 97.0 (C_3), 62.3 (OCH_2), 44.1 (C_{7a}), 37.6 (C_{3a}), 29.7 (C_7), 27.2 (NCH_3), 26.0 (C_4), 16.8 (CH_3), 15.3 (CH_3CH_2O); exact mass calcd for $C_{12}H_{19}NO_2$ 209.1416, found 209.1415.

2,4α-Dimethyl-3β-ethoxy-2,3,3aβ,4,7,7aβ-hexahydro-1H-isoindol-1-one (22). R_f 0.34 (EtOAc); IR 1680; ^{1}H NMR (250 MHz) δ5.77 (m, H_6), 5.58 (m, H_5), 4.47 (d, J=2.8 Hz, H_3), 3.46 (m, OCH_2), 2.84 (m, H_{7a}), 2.73 (s, NCH_3), 2.39-2.51 (m, H_{3a}, H_7), 2.30 (m, H_4), 1.97 (m, H_7), 1.10-1.24 (d,t, J=7 Hz, 2xCH_3); ^{13}C NMR (50 MHz) δ176.8 (C_1), 134.0 (C_5), 128.5 (C_6), 92.7 (C_3), 61.7 (OCH_2), 43.0 and 41.1 (C_{7a}, C_{3a}), 29.5 (C_4), 27.4 (NCH_3), 24.2 (C_7), 16.6 (CH_3), 15.4 (CH_3CH_2O); exact mass calcd for $C_{12}H_{19}NO_2$ 209.1416, found 209.1413.

Reduction of imide 8. From 1.5 g (8.4 mmol) of 8 was obtained 1.77 g of crude product after a reduction of 4 h and an ethanolysis period of 21 h. This material showed two spots on TLC, which were separated to afford 1.32 g (6.4 mmol, 74%) of less polar product and 110 mg (0.54 mmol, 6%) of more polar product. ^{13}C NMR showed that both components were about 1:1 mixtures of isomers. Data for these products: 2,5-dimethyl-3β-ethoxy-2,3,3aβ,4,7,7aβ-hexahydro-1H-isoindol-1-one (23) and its 2,6-dimethyl isomer 23a: R_f 0.38 (EtOAc): IR 1685; ^{1}H NMR (250 MHz) δ5.40 (m, 1H), 4.32 (s, H_3), 3.50 (m, 2H), 2.85 (s, 3H), 2.83 (m, 1H), 2.29-2.47 (m, 2H), 2.04-2.22 (2H), 1.71 (m, 1H), 1.65 (br s, 3H), 1.21 and 1.20 (2xt, J=7Hz, 3H); ^{13}C NMR (50 MHz) δ176.8 and 176.7 (C_1), 134.6 and 132.4 (C_6 of 23 and C_5 of 23a), 120.3 and 118.5 (C_5 of 23 and C_6 of 23a), 96.41 and 96.37 (C_3), 62.74 and 62.73 (OCH_2), 38.1, 37.1, 36.4 and 35.5 (C_{3a}, C_{7a}), 30.3, 27.0, 25.7 and 22.6 (C_4, C_7), 28.2 (NCH_3), 23.6 and 23.3 (CH_3), 15.3 (CH_3CH_2O); exact mass calcd for $C_{12}H_{19}NO_2$ 209.1416, found 209.1419. The corresponding 3α-ethoxy isomers 24 and 24a: R_f 0.23 (EtOAc); IR 1680; ^{1}H NMR (250 MHz) δ5.40 (m, 1H), 4.70 (d, J=5.5 Hz, H_3), 3.62 (m, 2H), 2.81 (s, 3H), 2.63 (m, ½H), 2.40-2.53 (m, 1½H), 2.16-2.29 (m, 2H), 1.83-2.11 (m, 2H), 1.67 (br s, 3H), 1.22 and 1.21 (2xt, J=7 Hz, 3H); ^{13}C NMR (50 MHz) δ176.3 and 175.9 (C_1), 133.5 and 132.8 (C_6 of 24 and C_5 of 24a), 93.0 and 92.8 (C_3), 65.9 and 65.5 (OCH_2), 39.6 and 38.5 (C_{7a}), 35.0 and 34.1 (C_{3a}), 27.8, 25.6, 23.6 and 20.9 (C_4, C_7), 27.4 and 27.3 (NCH_3), 23.4 (CH_3), 15.44 and 15.38 (CH_3CH_2O); exact mass calcd for $C_{12}H_{19}NO_2$ 209.1416, found 209.1407.

Reduction of imide 7. From 1.92 g (10.6 mmol) of 7 was obtained after reduction (2 h) and ethanolysis (18 h) 1.62 g of a mixture of ethoxy lactams 25 and 26 (7.7 mmol, 72%). The product ratio 92:8 (see Table II) was determined by integration of the signals for H_3 in the ^{1}H NMR spectrum of this mixture. Careful chromatography provided virtually pure 2,7α-dimethyl-3β-ethoxy-2,3,3aβ,4,5,6,7,7aβ-octahydro-1H-isoindol-1-one (25); R_f 0.64 (EtOAc)/acetone 1:1, IR 1680; ^{1}H NMR (250 MHz): δ4.16 (s, H_3), 3.49 (q, J=7 Hz, OCH_2), 2.81 (s, NCH_3), 2.71 (t, J=6 Hz, H_{7a}), 2.15 (dt, J=12, 6 Hz, H_{3a}), 1.47-1.74 (m, 4H), 1.28 (d, J=7 Hz, CH_3), 1.24 (m, H_{6e}), 1.18 (t, J=7 Hz, CH_3), 0.86-1.06 (m, H_{4a}, H_{5a}); ^{13}C NMR (50 MHz): δ175.9 (C_1), 95.0 (C_3), 63.4 (OCH_2), 43.7 (C_{7a}), 39.8 (C_{3a}), 32.0 (C_7), 30.8 (C_6), 28.3 (NCH_3), 26.7 and 24.3 (C_4, C_5), 18.7 (CH_3), 15.3 (CH_3CH_2O); exact mass calcd for $C_{12}H_{21}NO_2$ 211.1573, found 211.1572. Isomer 26 could not be obtained pure. It showed the following ^{1}H NMR data (250 MHz); δ4.59 (d, J=5 Hz, H_3), 2.85 (s, NCH_3).

Reduction of imide 9. From 2.24 g (12.4 mmol) of 9 (as a 5:1 mixture with its methyl epimer) was obtained after reduction (2 h) and ethanolysis (48 h) 1.74 g of a mixture of ethoxy lactams (8.2

mmol, 66%). The product ratio, determined by integration of the signals for H_3 the ^1H NMR spectrum of this mixture, was 61% (4.20 ppm, J=OHz): 5% (4.69 ppm, J=5.5 Hz). The major component was obtained pure through chromatography. However, ^{13}C NMR of this supposedly pure component showed it to be an about 9:1 mixture of isomers. We surmise that the minor isomer of this mixture has arisen from the methyl epimer of 9. It has to be noted that neither the structure of this minor isomer, nor the structure of 28 has been rigorously proved. The structure of 27 is certain: 2,5α-dimethyl--3β-ethoxy-2,3,3aβ,4,5,6,7,7aβ-octahydro-1H-isoindol-1-one (27): R_f 0.43 (EtOAc/hexane 1:1); IR 1685; ^1H NMR (250 MHz): δ4.20 (s, H_3), 3.51 (q, J=7 Hz, OCH_2), 2.88 (s, NCH_3), 2.69 (m, H_{7a}), 2.29 (dt, J=12 Hz, 6 Hz, H_{3a}), 2.20 (m, H_7), 1.71 (m, $H_{4\beta}$), 1.36-1.55 (m, $H_{6\beta}$,$H_{7\beta}$), 1.31 (m, H_5), 1.20 (t, J=7 Hz, CH_3), 0.81 (d, J=7 Hz, CH_3), 0.71 (m, $H_{6\alpha}$), 0.54 (apparent q, J=12.5 Hz, $H_{4\alpha}$), the high field signal (δ.54 ppm) is particularly diagnostic for an axial hydrogen of a methylene group between two carbon atoms bearing equatorial alkyl groups;[38] ^{13}C NMR (50 MHz) δ176.3 (C_1), 95.5 (C_3), 63.2 (OCH_2), 38.5 and 37.8 (C_{3a}, C_{7a}), 36.0 and 31.2 (C_6, C_4), 29.9 (C_5), 28.6 (NCH_3), 22.6 (C_7), 22.4 (CH_3), 15.2 (CH_3CH_2O); exact mass calcd for $C_{12}H_{21}NO_2$ 211.1573, found 211.1569.

Reduction of imide 12. From 650 mg (2.2 mmol) of 12 was obtained after reduction (1.5 h) and ethanolysis (6 h) 750 mg of a yellow oil, which on chromatography provided 547 mg (1.65 mmol, 75%) of a single product as a colourless oil which became crystalline in the freezer: 5,5-ethylene--dithio-3β-ethoxy-2-methyl-2,3,3aβ,4,5,6,7,7aβ-octahydro-1H-isoindol-1-one (29): R_f 0.27 (EtOAc); IR 3440, 1685; ^1H NMR (250 MHz) δ4.19 (s, H_3), 3.76 (m, CH_2OH), 3.53 (m, CH_2O), 3.27 (s, CH_2S), 2.97 (t, J=6 Hz, H_{7a}), 2.83 (s, NCH_3), 2.49 (dt, J=12, 6 Hz, H_{3a}), 2.36 (m, H_7), 2.06-2.27 (m, $H_{4\beta}$, $CHHCH_2OH$), 2.06 (br s, OH), 1.99 (dd, J=13, 2 Hz, $H_{6\beta}$), 1.81 (m, $CHHCH_2OH$), 1.74 (dd, J=13, 12 Hz, $H_{4\alpha}$), 1.55 (dd, J=13, 12 Hz, $H_{6\alpha}$), 1.20 (t, J=7 Hz, CH_3); ^{13}C NMR (63 MHz): δ175.5 (C_1), 94.4 (C_3), 66.8 (CH_2CH_2O), 63.8 (C_5), 61.2 (CH_2OH), 45.5 and 43.2 (CH_2S), 40.1 and 39.5 (C_{3a}, C_{7a}) 39.3 and 38.1 (C_4, C_6), 34.8 (CH_2CH_2OH), 34.3 (C_7), 28.5 (NCH_3), 15.3 (CH_3CH_2); exact mass calcd for $C_{15}H_{25}NO_3S_2$ 331.1276, found 331.1260.

7α-{2-[(tert-Butyldimethylsilyl)oxy]}ethyl-5,5-ethylenedioxo-3α-hydroxy-2-methyl-2,3,3aβ,4,5,6,7,-7aβ-octahydro-1H-isoindol-1-one (32). To a stirred solution of 142 mg (0.37 mmol) of imide 13 in 3 ml of ethanol was added at 0°C all at once 100 mg (2.64 mmol) of $NaBH_4$. The mixture was stirred at 0°C, while every 15 min three drops of a 0.5N solution of H_2SO_4 in ethanol was added. The reaction was followed by TLC and was complete after 70 min. The mixture was then poured out into 10 ml of ice water and extracted with chloroform (4x15 ml). The combined organic solutions were washed with brine (10 ml), dried (K_2CO_3) and concentrated in vacuo. The residue was chromatographed to furnish 89 mg (0.23 mmol, 62%) as the only isolable product, which crystallized from EtOAc: mp 115-117°C; R_f 0.31 (EtOAc); IR 3380, 1680, 1255, 840; ^1H NMR (250 MHz): δ5.03 (dd, J=10, 6 Hz, H_3), 3.92 (br s, $O(CH_2)_2O$), 3.69 (m, CH_2OSi), 3.45 (d, J=10 Hz, OH), 2.77 (s, NCH_3), 2.75 (m, H_7), 2.56 (m, H_{7a}), 2.09-2.18 (m, H_7, $CHHCH_2OSi$), 1.70-1.86 (m, $H_{4\beta}$, $H_{6\beta}$, $CHHCH_2OSi$), 1.63 (dd, J=14, 8.5 Hz, $H_{4\alpha}$), 1.43 (dd, J=13.5, 13 Hz, $H_{6\alpha}$), 0.86 (s, $C(CH_3)_3$), 0.02 (s, $Si(CH_3)_2$); ^{13}C NMR (63 MHz); δ173.5 (C_1), 108.9 (C_5), 83.8 (C_3), 64.3 and 64.1 (OCH_2CH_2O), 61.0 (CH_2OSi), 42.8, 38.2 and 37.6 (C_{3a}, C_{7a}, C_7), 34.9, 30.4, 29.9 and 25.9 (C_4, C_6, CH_2CH_2OSi and NCH_3), 25.8 ($C(CH_3)_3$), 18.1 ($C(CH_3)_3$), -5.5 ($Si(CH_3)_2$); exact mass calcd for $C_{15}H_{26}NO_5Si$ (M^+-$C(CH_3)_3$) 328.1610, found 328.1595.

Methylation of hydroxy lactam 32. To 38 mg of a sodium hydride suspension in oil (50-55%, containing 19 mg (0.8 mmol) of NaH) was added under nitrogen 0.7 ml of THF and then dropwise a solution of 136 mg (0.35 mmol) of 32 in 1 ml of THF. The mixture was stirred for 15 min and then treated with 0.8 ml (1.82 g, 12.8 mmol) of methyl iodide. TLC showed that the methylation was complete after 70 min. The reaction mixture was diluted with 5 ml of saturated aqueous $NaHCO_3$ and then extracted with chloroform (3x20 ml). The combined organic solutions were dried (K_2CO_3) and concentrated in vacuo to afford 134 mg of yellow oil. Chromatography gave the two methoxy lactams in pure state as colourless oils. 30: 90 mg (0.23 mmol, 64%); R_f 0.45 (EtOAc); IR 1690, 1255, 840; ^1H NMR (250 MHz): δ4.12 (s, H_3), 3.92 (s, OCH_2CH_2O), 3.70 (t, J=6 Hz, CH_2OSi), 3.35 (s, OCH_3), 2.86 (s, NCH_3), 2.78 (m, H_{7a}), 2.48 (dt, J=12, 6 Hz, H_{3a}), 2.11-2.30 (m, H_7, $CHHCH_2OSi$), 1.72-1.97 (m, $H_{4\beta}$, $CHHCH_2OSi$), 1.64 (m, $H_{6\beta}$), 1.17-1.37 (m, $H_{4\alpha}$, $H_{6\alpha}$), 0.88 (s, $C(CH_3)_3$), 0.02 (s, $Si(CH_3)_2$). 31: 23 mg (0.058 mmol, 16%); R_f 0.52 (EtOAc); IR 1690, 1255, 835; ^1H NMR (250 MHz) δ4.57 (d, J=5 Hz, H_3), 3.91 (s, OCH_2CH_2O), 3.67 (t, J=6 Hz, CH_2OSi), 3.39 (s, OCH_3), 2.72 (s, NCH_3), 2.72 (m, H_{7a}), 2.46 (m, H_{3a}), 1.17-2.26 (m, 7H), 0.89 (s, $C(CH_3)_3$), 0.03 (s, $Si(CH_3)_2$).

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