Pergamon

Tetrahedron 57 (2001) 2581–2588

TETRAHEDRON

# Synthesis of 3-alkyl-1-isoindolinones by alkylation of a benzotriazolyl substituted *N*-dimethylamino-phthalimidine

Eric Deniau[†] and Dieter Enders[*]

*Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule, Professor-Pirlet-Straße 1, 52074 Aachen, Germany*

Dedicated to Professor H. B. Kagan

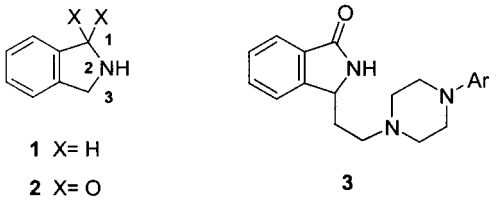
Received 1 August 2000; accepted 2 October 2000

**Abstract**—A convenient and versatile synthesis of 3-alkyl-2,3-dihydro-1*H*-isoindol-1-ones (isoindolinones) based upon sequential metalation, alkylation alpha to nitrogen and *C*,*N*-deprotection from 3-benzotriazolyl-2-dimethylamino-phthalimidine is described. 

## 1. Introduction

Functionalisation alpha to nitrogen in a number of acyclic systems or saturated heterocycles has attracted considerable attention over the years. Groups that have tackled this challenge have adopted cation methodology[1] or radical chemistry,[2] although methods based on carbanion chemistry are still the most general routes for electrophilic substitution alpha to nitrogen.[3] This approach depicted in Scheme 1 provides a powerful general strategy for the elaboration of amine derivatives by Umpolung (polarity inversion) of the customary amine reactivity.[4]

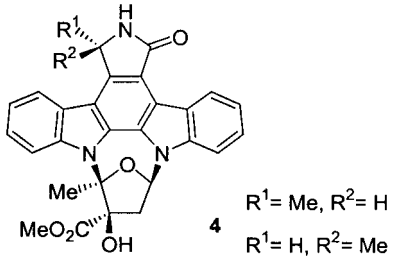
In this general sequence a group G is connected to the amine in order to facilitate the deprotonation step and avoid a possible competitive metalation reaction at the nitrogen atom. In general, this group must be stable towards strong bases, must not interfere with the electrophilic substitution and must be conveniently removed in the last step. Whereas considerable efforts have been devoted to apply this strategy to the synthesis of numerous mono- and bicyclic amines, such as pyrrolidines, piperidines, indols or isoquinolines, only a few papers report on the sequential alkylation of compounds possessing an isoindol skeleton. To the best of our knowledge, only tetrahydro derivatives **1** (X=H) bearing an oxazoline[5] or a formamidine[6] group have been subjected to the complete deprotonation, alkylation, deprotection sequence. In the case of the corresponding lactams **2** (X=O of carbonyl group) known as phthalimidines (2,3-dihydro-1*H*-isoindol-1-ones or 1-isoindolinones) only the first two steps have been exemplified,[7] probably owing to the presence of a carbonyl function and a benzylic position adjacent to nitrogen in these sensitive models, which render both connection and disconnection of the metalation auxiliary problematic.




**1** X= H

**2** X= O

**3**




**4**

$R^1$= Me, $R^2$= H

$R^1$= H, $R^2$= Me

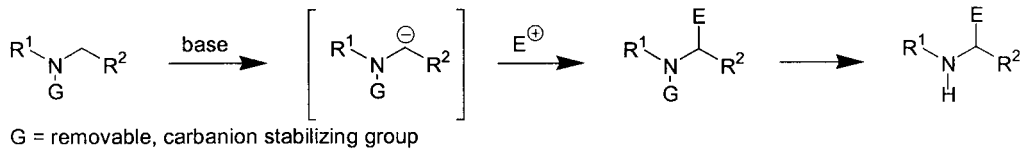
In recent years, 3-substituted-isoindolinones have elicited a certain interest in the scientific community since they represent the core unit of numerous naturally occurring substances[8] and several members belonging to this family have shown interesting biological properties.[9] For example, piperazine derivatives **3** and indolocarbazoles **4** have been recently reported to display a high affinity for dopamine receptors[10] and proteine kinase activity, respectively.[11] Paradoxically, in spite of extensive work in this field, few general methodologies have been developed to synthesize these heterobicyclic compounds. Isoindolinones are accessible by different chemical processes which include (i) rearrangement of six membered rings.[12] (ii) Elimination reactions from 3,3-disubstituted compounds.[13] (iii) The

*Keywords*: alkylation; benzotriazole; carbanions; hydrazines; lactams.

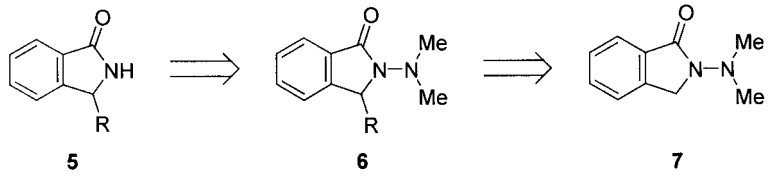
* Corresponding author. Fax: +49-0-241-8888-127; e-mail: enders@rwth-aachen.de

† On leave from UST Lille 1 F-59655 Villeneuve d'Ascq Cedex.

0040–4020/01/$ - see front matter 
PII: S0040-4020(01)00073-4




**Scheme 1.**




**Scheme 2.**

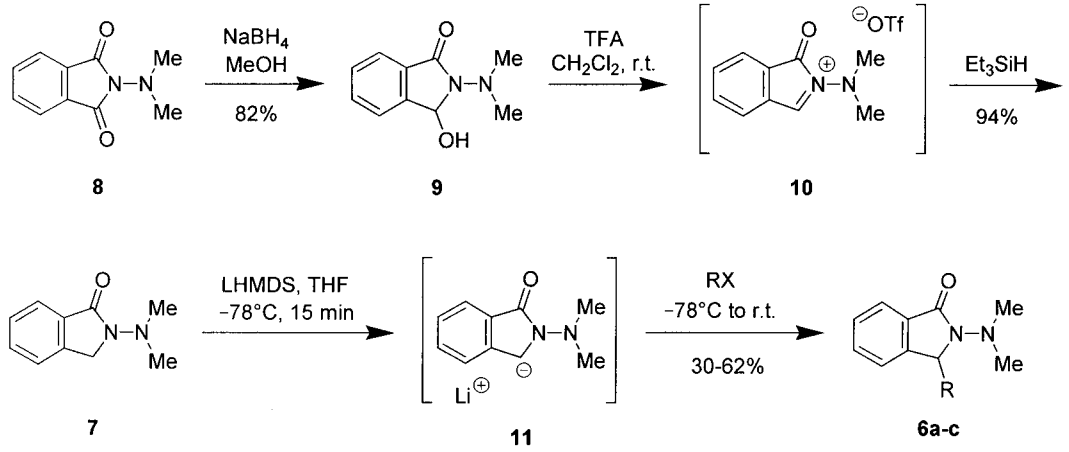
Parham protocol[14] or more recently a carbocationic pathway.[15] but the most commonly employed synthetic method[16] involves, in the final step, the construction of the lactam unit from a elaborated benzenic precursor. However, these methods are rather restricted in scope and do not permit an efficient functionalisation at the three position of the lactam ring.

## 2. Results and discussion

These different limitations led us to propose the following retrosynthetic analysis (Scheme 2), in which the key step consists in the sequential alkylation of the parent phthalimidine **7** bearing an appropriate protecting group on the nitrogen atom of the lactam unit. This kind of strategy should offer the potential advantage of facilitating incorporation of substituents alpha to nitrogen within the heterocyclic ring via **6** leading to the title compounds **5**.

Critical to the success of our strategy was therefore to identify an auxiliary group, which would be sufficiently robust to survive the intended metalation step and would be also labile enough to be removed in the final step in order to regenerate the lactam nucleus. This dual requirement prompted us to incorporate the dimethylamino group in the parent model **7**. Indeed, the ability of this group to direct carbanion formation alpha to nitrogen has been reported by Grieco et al.,[17] who have studied the functionalisation of the pyrrol nucleus at C(2) position via a metalation pathway. On the other hand, the choice of the dimethylamino group was dictated by the properties of the N–N bond, present in these *N*-acyl hydrazines (hydrazides), which is well known to be cleaved under various conditions.[18] This synthetic route necessitated the preliminary elaboration of the lactam **7**. The synthesis of this *N*-amino lactam proved to be unexpectedly difficult. Indeed, in contrast to the known synthesis of 2-alkyl or 2-aryl phthalimidines via different synthetic pathways,[19] elaboration of their 2-amino analogues seems rather problematic. The condensation between differently substituted hydrazines and a phthalide derivative[20] or an *o*-halogenomethylbenzoic acid ester[21] has been reported, but always in moderate yields. The lack of efficiency of these synthetic approaches led us to investigate a new reaction pathway depicted in Scheme 3. This new approach is based on the chemoselective mono reduction of the phthalimide **8** and involves, as the key step, the reduction of the transient iminium ion **10**.

We found that the imide **8**, easily prepared by condensation between phthalic anhydride and dimethylhydrazine,[22] could be readily reduced with $NaBH_4$ to give the 3-hydroxy derivative **9**. Exposure of this *N*,*O*-hemiacetal to trifluoroacetic acid then induced the formation of the iminium salt




**Scheme 3.**

**Table 1.** Sequential alkylation of **7**

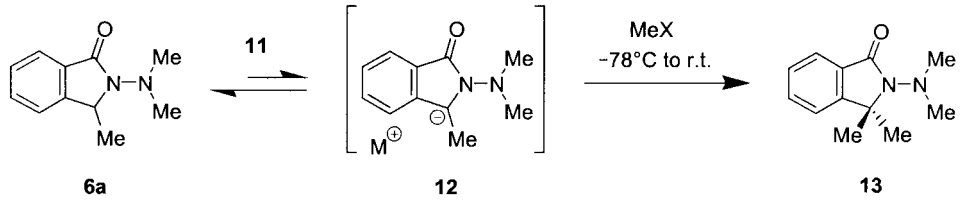
| Entry | Compound | LHMDS (equiv.) | RX (equiv.) | Yield (%) |
|---|---|---|---|---|
| 1 | **6a** | 1.1 | $Me_2SO_4$ (1.1) | 30 |
| 2 | **6a** | 1.1 | MeBr (1.1) | 42 |
| 3 | **6a** | 1.1 | MeI (1.1) | 62 |
| 4 | **6a** | 1.1 | MeI (2.0) | 48 |
| 5 | **6b** | 1.1 | EtI (1.1) | 55 |
| 6 | **6c** | 1.1 | PrI (1.1) | 46 |

**10**, which was reduced in situ with $Et_3SiH$[23] to afford the desired 2-(dimethylamino)-isoindolinone **7** in a yield of 77% over two steps. In order to evaluate the influence of both stoichiometry and the nature of the electrophile on the alkylation step, phthalimidine **7** was deprotonated under optimized conditions with lithium hexamethyldisilazide (LHMDS, 1.1 equiv./THF/−78°C/15 min) and then quenched by various alkyl halides (Scheme 3, Table 1). Unfortunately, whatever conditions were used, the desired alkylated products **6** were always obtained in low to moderate yields.

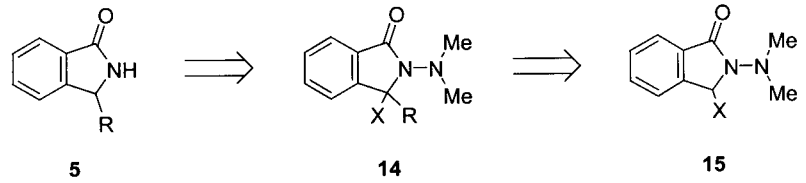
While more reactive alkyl iodides permitted a slight improvement in terms of yields (entries 1–3), further experiments by changing the solvent, the reaction time or use of a metalation additive, were unrewarding. In addition, a qualitative analysis of the methylation reaction (entry 2) showed the presence of starting material **7** in the crude reaction product, in addition to mono and dialkylated isoindolinones **6a** and **13**, respectively (Scheme 4), which rendered purification steps particularly problematic. These results can be rationalized, in part, if we consider a possible transmetalation reaction between the monomethylated product **6a** and the preliminary formed carbanion **11** to give **12** faster than the alkylation step.

In order to circumvent these difficulties, we modified the pattern of our model without changing the strategy by connecting a temporary protecting group X at the 3-position of the phthalimidine nucleus via **15** and **14** as depicted in the retrosynthetic Scheme 5.

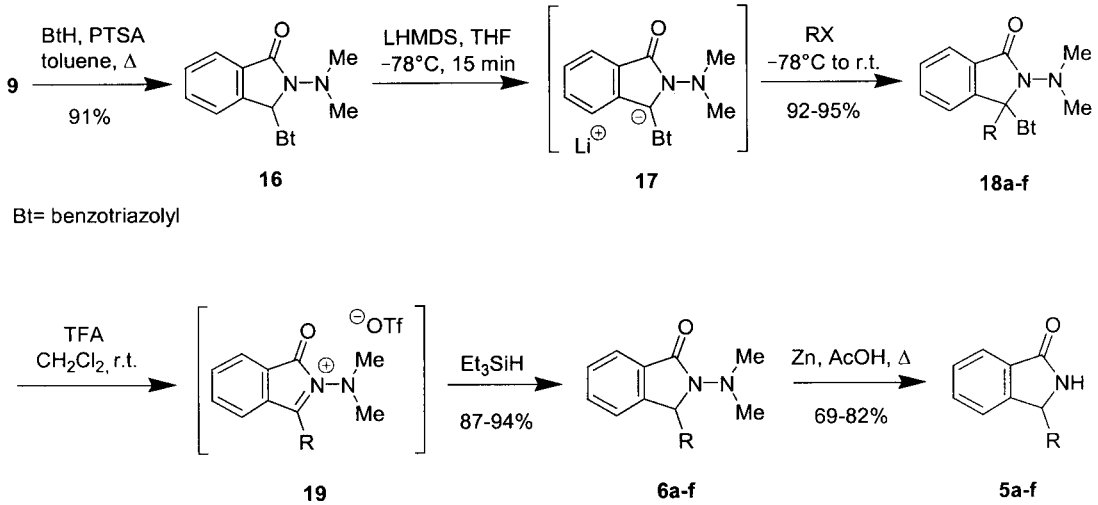
To assure the viability of this new methodology, it was necessary to find a protecting group easily introduced, compatible with the metalation conditions and most importantly, easy to remove in the final step. Katritzky and coworkers[24] reported the regioselective lithiation of numerous aminals at the methylene bridge linking an heterocyclic




**Scheme 4.**




**Scheme 5.**




**Scheme 6.**

**Table 2.** Preparation of compounds **18**, **6** and **5**

| | RX | **18** (Yield %) | **6** (Yield %) | **5** (Yield %) |
|---|---|---|---|---|
| **a** | MeI | 90 | 94 | 76 |
| **b** | EtI | 93 | 91 | 69 |
| **c** | PrI | 94 | 89 | 71 |
| **d** | BuI | 92 | 90 | 78 |
| **e** | HexI | 91 | 87 | 73 |
| **f** | BnBr | 95 | 94 | 80 |

amine and a benzotriazole moiety and demonstrated the possibility to remove this metalation auxiliary under reductive conditions. These results led us to investigate the possibility to use the benzotriazolyl group to protect the benzylic position in our model in the synthetic sequence depicted in Scheme 6.

The parent phthalimidine **16** was readily prepared from the carbinolamine **9** after treatment with an excess of benzotriazole under catalytic acidic conditions (*p*-toluenesulfonic acid, PTSA) and was then smoothly deprotonated with LHMDS in THF at −78°C to give the corresponding α-metalloamine **17**. This carbanionic species was then allowed to react with an array of alkyl halides to afford excellent yields of the 3,3-disubstituted-1-isoindolinones **18a–f** (Table 2).

In order to carry out the C(3)-deprotection of these aminals, benzotriazole being a well known leaving group owing to its electron withdrawing nature, we anticipated that it could be possible to remove this auxiliary under acidic conditions in the presence of a carbocation scavenger. Gratifyingly, treatment of compounds **18a–f** with an excess of trifluoroacetic acid gave the transient iminium ions **19**, which were successfully reduced with triethylsilane to afford the desired 3-alkylated-1-isoindolinones **6a–f**. Finally, removal of the *N*-dimethylamino group in compounds **6a–f** was achieved cleanly by heating with excess of zinc in refluxing acetic acid.[25] This protocol delivered the targeted 3-alkyl phthalimidines **5a–f** in good yields.

## 3. Conclusions

By means of a new synthetic approach involving as the key step the alkylation of an α-aminocarbanion derived from a cyclic hydrazide, we have disclosed a concise and efficient synthesis of 3-alkyl-1-isoindolinones. Owing to the efficiency and simplicity of the new methodology, this protocol shows potential for further development and work aimed at performing these reactions with asymmetric induction are currently under investigation.

## 4. Experimental

### 4.1. General

$^1$H (300 MHz) and $^{13}$C NMR (75 MHz) spectra were recorded on a Varian VXR 300 (solvent $CDCl_3$, TMS as internal standard). Chemical shifts are expressed in ppm. Abbreviations used are s (singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet) and br. (broad). Mass spectra were registered on a Varian MAT 212 (EI 70 eV) with DIE ionisation. IR spectra were registered on a Perkin–Elmer FT/IR 1750. Preparative column chromatography: Merck silica gel 60, particle size 0.040–0.063 mm (230–400 mesh, flash). Analytical TLC: silica gel 60 $F_{254}$ plates, Merck, Darmstadt. All melting points (Büchi apparatus, system Dr. Tottoli) are uncorrected. Microanalyses were obtained with a Heraeus CHN-O-RAPID element analyser. Tetrahydrofuran (THF) was freshly distilled over Na and dichloromethane ($CH_2Cl_2$) over $CaH_2$.

**4.1.1. Synthesis of 2-(dimethylamino)-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one (9).** Phthalimide **8** (15 g, 79 mmol) was dissolved in absolute MeOH (150 ml) and carefully treated with $NaBH_4$ (3.3 g, 87 mmol) under $N_2$ in a ice-cooled flask. The mixture was stirred for additional 30 min, saturated aqueous $NH_4Cl$ solution was added and the MeOH was removed under vacuum. The crude product was extracted with $CH_2Cl_2$ (3×100 ml) which was then dried over $Na_2SO_4$. Evaporation of the solvent furnished an oily product, which slowly solidified on standing and afforded the 3-hydroxy derivative **9** (12.4 g, 82%) which was then used in the next step without further purification. **9**: mp 85–86°C; $^1$H NMR $\delta$ 3.08 (s, 6H, $NMe_2$), 5.52 (d, $J$=8.0 Hz, 1H, NCHAr), 5.76 (d, $J$=8.0 Hz, 1H, OH), 7.33–7.50 (m, 3H, $H_{arom}$), 7.54–7.59 (m, 1H, $H_{arom}$); $^{13}$C NMR *C* 166.1 (CO), 142.0, 131.0, *CH* 132.4, 129.6, 123.3, 122.9, 81.0, $CH_3$ 44.7. *m/z* (%): 192 ($M^+$, 36), 150 (56), 133 (67), 105 (37), 59 (100). IR (KBr) 1701 (CO), 3285, 3097. Anal. calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.83; H, 6.11; N, 14.69.

**4.1.2. Synthesis of 2-(dimethylamino)-2,3-dihydro-1*H*-isoindol-1-one (7).** A solution of compound **9** (11.6 g, 60.4 mmol) in a mixture of trifluoroacetic acid (10 ml) and $CH_2Cl_2$ (30 ml) was stirred under argon and cooled with an ice bath. The solution was then treated with triethylsilane (12 ml, 75 mmol). After removal of the ice-bath, the stirring was continued for 1 h. The mixture was then poured into ice-water, made alkaline by the addition of solid $K_2CO_3$ and extracted with $CH_2Cl_2$ (3×100 ml). The extracts were combined, dried over $Na_2SO_4$ and evaporated under vacuum. The oily residue was chromatographed on a $SiO_2$ column using acetone/hexane as eluent (50:50) and finally recrystallized from pentane–toluene to afford isoindolinone **7** (10.0 g, 94%) as pale yellow solid. **7**: mp 133–134°C; $^1$H NMR $\delta$ 2.68 (s, 6H, $NMe_2$), 4.32 (s, 2H, $NCH_2Ar$), 7.13–7.46 (m, 3H, $H_{arom}$), 7.73 (d, $J$=7.8 Hz, 1H, $H_{arom}$); $^{13}$C NMR *C* 166.3 (CO), 139.2, 132.0, *CH* 131.4, 127.9, 123.5, 122.6, $CH_2$ 43.8, $CH_3$ 44.2. *m/z* (%): 176 ($M^+$, 46), 134 (100). IR (KBr) 1676 (CO). Anal. calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 67.92; H, 6.91; N, 16.22.

### 4.2. General procedure for the alkylation of phthalimidine 7

A solution of LHMDS (1 M in hexane, 1.1 equiv.) was added dropwise to a solution of **7** (528 mg, 3 mmol) in THF (50 ml) at −78°C under $N_2$. The yellow solution was stirred for 15 min and then the alkylating agent was added. The mixture was allowed to warm to room temperature and treated with a saturated $NH_4Cl$ aqueous solution (20 ml).

After extraction with $Et_2O$ (2×50 ml), the organic layer was dried over $Na_2SO_4$. Evaporation of the solvent gave the alkylated products, which were carefully chromatographed on a $SiO_2$ column using acetone/hexane (40:60) as eluent.

**4.2.1. 2-(Dimethylamino)-3-methyl-2,3-dihydro-1*H*-isoindol-1-one (6a).** Oil; $^1$H NMR $\delta$ 1.48 (d, $J$=6.6 Hz, 3H, Me), 2.97 (s, 6H, $NMe_2$), 4.45 (q, $J$=6.6 Hz, 1H, NCHAr), 7.32 (d, $J$=7.8 Hz, 1H, $H_{arom}$), 7.37–7.42 (m, 1H, $H_{arom}$), 7.46–7.53 (m, 1H, $H_{arom}$), 7.75 (d, $J$=7.7 Hz, 1H, $H_{arom}$); $^{13}$C NMR *C* 166.9 (CO), 145.5, 131.8, *CH* 131.6, 128.0, 123.1, 122.0, 57.0, $CH_3$ 44.4, 17.9. *m/z* (%): 190 ($M^+$, 23), 148 (100), 132 (34). IR (KBr) 1694 (CO), 1767. Anal. calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.72. Found: C, 69.40; H, 7.56; N, 14.79.

**4.2.2. 2-(Dimethylamino)-3,3-dimethyl-2,3-dihydro-1*H*-isoindol-1-one (13).** Mp 134–135°C; $^1$H NMR $\delta$ 1.48 (s, 6H, 2Me), 3.01 (s, 6H, $NMe_2$), 7.31–7.35 (m, 1H, $H_{arom}$), 7.40 (dt, $J$=7.7, 1.1 Hz, 1H, $H_{arom}$), 7.52 (dt, $J$=7.7, 1.4 Hz, 1H, $H_{arom}$), 7.75–7.79 (m, 1H, $H_{arom}$); $^{13}$C NMR *C* 166.1 (CO), 150.2, 130.6, 63.5, *CH* 131.7, 127.8, 123.2, 120.9, $CH_3$ 45.1, 24.7. *m/z* (%): 204 ($M^+$, 35), 189 (19), 175 (27), 162 (100), 146 (80). IR (KBr) 1683 (CO). Anal. calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.69; H, 7.74; N, 13.92.

**4.2.3. 2-(Dimethylamino)-3-ethyl-2,3-dihydro-1*H*-isoindol-1-one (6b).** Oil; $^1$H NMR $\delta$ 0.72 (t, $J$=7.4 Hz, 3H, Me), 1.90–2.13 (m, 2H, $CH_2$), 2.97 (s, 6H, $NMe_2$), 4.43 (t, $J$=4.7 Hz, 1H, NCHAr), 7.31–7.44 (m, 2H, $H_{arom}$), 7.49 (dt, $J$=7.4, 1.4 Hz, 1H, $H_{arom}$), 7.75 (d, $J$=7.4 Hz, 1H, $H_{arom}$); $^{13}$C NMR *C* 167.7 (CO), 143.6, 132.5, *CH* 131.4, 127.9, 123.1, 122.2, 61.7, $CH_2$ 23.3, $CH_3$ 44.0, 7.6. *m/z* (%): 205 ($M^+$, 70), 162 (81), 146 (26), 132 (67). IR (KBr) 1697 (CO). Anal. calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.40; H, 7.85; N, 13.94.

**4.2.4. 2 (Dimethylamino)-3-propyl-2,3-dihydro-1*H*-isoindol-1-one (6c).** Mp 54–55°C; $^1$H NMR $\delta$ 0.81 (t, $J$=7.3 Hz, 3H), 0.88–1.08 (m, 1H), 1.09–1.31 (m, 1H), 1.72–1.86 (m, 1H), 1.911–2.04 (m, 1H), 2.98 (s, 6H, $NMe_2$), 4.57 (dd, $J$=6.3, 3.8 Hz, 1H, NCHAr), 7.27–7.40 (m, 2H, $H_{arom}$), 7.49 (dt, $J$=7.7, 1.4 Hz, 1H, $H_{arom}$), 7.71 (d, $J$=8.0 Hz, 1H, $H_{arom}$); $^{13}$C NMR *C* 167.6 (CO), 143.8, 132.6, *CH* 131.6, 128.1, 123.2, 122.2, 61.2, $CH_2$ 31.9, 16.6, $CH_3$ 44.1, 14.1. *m/z* (%): 218 ($M^+$, 30), 176 (100), 146 (80), 132 (57). IR (KBr) 1700 (CO). Anal. calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.59; H, 8.05; N, 12.98.

**4.2.5. Synthesis of the 3-(1*H*-1,2,3-benzotriazol-1-yl)-2-(dimethylamino)-3-methyl-2,3-dihydro-1*H*-isoindol-1-one (16).** To a suspension of benzotriazole (6.8 g, 57.2 mmol) and hydroxyphthalimidine **9** (10 g, 52.1 mmol) in toluene (200 ml) was added *p*-toluenesulfonic acid (100 mg). The mixture was refluxed for 3 h while removing the reaction water with a Dean–Stark trap. The solution was then cooled, washed with a saturated aqueous solution of $NaHCO_3$ (25 ml) and dried over $Na_2SO_4$. After removal of the solvent, the crude compound was recrystallized from hexane–toluene to afford **16** (13.9 g, 91%) as a colourless solid. **16**: mp 150–151°C; $^1$H NMR $\delta$ 2.68 (s, 6H, $NMe_2$), 6.60 (d, $J$=8.4 Hz, 1H, $H_{arom}$), 7.22–7.38 (m, 3H, $H_{arom}$), 7.39 (s, 1H, NCHN), 7.55–7.71 (m, 2H, $H_{arom}$), 7.99–8.05 (m, 1H, $H_{arom}$), 8.07–8.13 (m, 1H, $H_{arom}$); $^{13}$C NMR *C* 166.1 (CO), 151.7, 146.9, 137.8, 131.4, *CH* 133.3, 130.9, 128.0, 124.5, 123.9, 123.6, 120.5, 110.0, 72.0, $CH_3$ 44.0. *m/z* (%): 293 ($M^+$, 78), 251 (38), 221 (100), 207 (40), 179 (37), 131 (55). IR (KBr) 1719 (CO). Anal. calcd for $C_{16}H_{15}N_5O$: C, 65.52; H, 5.15; N, 23.88. Found: C, 65.33; H, 5.19; N, 23.73.

### 4.3. General procedure for the alkylation of the 3-benzotriazolyl-isoindolinone 16

Isoindolinones **18a–f** were obtained following the same procedure as described for the alkylation of **7** but the final compounds were purified by recrystallisation from hexane–toluene.

**4.3.1. 3-(1*H*-1,2,3-benzotriazol-1-yl)-2-(dimethylamino)-3-methyl-2,3-dihydro-1*H*-isoindol-1-one (18a).** Mp 152–153°C; $^1$H NMR $\delta$ 2.42 (br. s, 9H, Me+$NMe_2$), 6.12 (d, $J$=8.3 Hz, 1H, $H_{arom}$), 6.96–7.06 (m, 1H, $H_{arom}$), 7.08–7.18 (m, 2H, $H_{arom}$), 7.41–7.56 (m, 2H, $H_{arom}$), 7.83–7.96 (m, 2H, $H_{arom}$); $^{13}$C NMR *C* 165.5 (CO), 146.6, 134.4, 131.3, 130.4, 79.9, *CH* 133.4, 130.6, 127.6, 124.1, 123.8, 122.4, 120.2, 110.7, $CH_3$ 44.7, 23.3. *m/z* (%): 307 ($M^+$, 15), 221 (24), 188 (26), 146 (79), 145 (100), 119 (37), 91 (45). IR (KBr) 1708 (CO). Anal. calcd for $C_{17}H_{17}N_5O$: C, 66.43; H, 5.58; N, 22.79. Found: C, 66.58; H, 5.62; N, 22.56.

**4.3.2. 3-(1*H*-1,2,3-benzotriazol-1-yl)-2-(dimethylamino)-3-ethyl-2,3-dihydro-1*H*-isoindol-1-one (18b).** Mp 172–173°C; $^1$H NMR $\delta$ 1.00 (t, $J$=7.4 Hz, 3H, $CH_3$), 2.65 (br. s, 6H, $NMe_2$), 3.20–3.35 (m, 1H, $CH_2$), 3.38–3.53 (m, 1H, $CH_2$), 6.21 (d, $J$=8.5 Hz, 1H, $H_{arom}$), 7.22–7.30 (m, 1H, $H_{arom}$), 7.36–7.46 (m, 2H, $H_{arom}$), 7.72–7.86 (m, 2H, $H_{arom}$), 8.15–8.22 (m, 2H, $H_{arom}$); $^{13}$C NMR *C* 166.0 (CO), 146.4, 141.2, 131.7, 131.5, 83.4, *CH* 133.2, 130.6, 127.6, 124.1, 123.8, 122.8, 120.2, 110.7, $CH_2$ 26.9, $CH_3$ 44.4, 8.0. *m/z* (%): 321 ($M^+$, 100), 249 (32), 234 (63), 221 (55), 220 (88), 206 (80), 178 (28), 160 (56). IR (KBr) 1709 (CO). Anal. calcd for $C_{18}H_{19}N_5O$: C, 67.27; H, 5.96; N, 21.79. Found: C, 67.33; H, 5.78; N, 21.50.

**4.3.3. 3-(1*H*-1,2,3-benzotriazol-1-yl)-2-(dimethylamino)-3-propyl-2,3-dihydro-1*H*-isoindol-1-one (18c).** Mp 178–179°C; $^1$H NMR $\delta$ 0.81–1.08 (m, 4H), 1.10–1.28 (m, 1H), 2.48 (br. s, 6H, $NMe_2$), 2.99–3.19 (m, 2H), 6.00 (d, $J$=8.2 Hz, 1H, $H_{arom}$), 7.05 (t, $J$=7.7 Hz, 1H, $H_{arom}$), 7.16–7.25 (m, 2H, $H_{arom}$), 7.51–7.64 (m, 2H, $H_{arom}$), 7.94 (d, $J$=7.4 Hz, 1H, $H_{arom}$), 7.98 (d, $J$=8.5 Hz, 1H, $H_{arom}$); $^{13}$C NMR *C* 165.9 (CO), 146.5, 141.6, 131.7, 131.4, 82.9, *CH* 133.2, 130.6, 127.6, 124.1, 123.8, 122.8, 120.3, 110.8, $CH_2$ 35.8, 16.9, $CH_3$ 44.4, 13.8. *m/z* (%): 335 ($M^+$, 100), 264 (26), 248 (39), 234 (57), 221 (48), 220 (80), 193 (41), 174 (63), 173 (63), 172 (83). IR (KBr) 1707 (CO). Anal. calcd for $C_{19}H_{21}N_5O$: C, 68.04; H, 6.31; N, 20.88. Found: C, 68.32; H, 6.28; N, 20.53.

**4.3.4. 3-(1*H*-1,2,3-benzotriazol-1-yl)-3-butyl-2-(dimethylamino)-2,3-dihydro-1*H*-isoindol-1-one (18d).** Mp 176–177°C; $^1$H NMR $\delta$ 0.81–1.04 (m, 4H), 1.06–1.26 (m, 1H), 1.32–1.50 (m, 2H), 2.47 (br. s, 6H, $NMe_2$), 2.99–3.29 (m, 2H), 6.02 (d, $J$=8.5 Hz, 1H, $H_{arom}$), 7.03–7.12

(m, 1H, $H_{arom}$), 7.18–7.27 (m, 2H, $H_{arom}$), 7.53–7.69 (m, 2H, $H_{arom}$), 7.90–8.06 (m, 2H, $H_{arom}$); $^{13}C$ NMR *C* 166.0 (CO), 146.4, 141.5, 131.6, 131.4, 82.9, *CH* 133.2, 130.8, 127.5, 124.0, 123.8, 122.9, 120.2, 110.7, $CH_2$ 33.5, 25.5, 22.5, $CH_3$ 44.4, 13.9. *m/z* (%): 349 ($M^+$, 6), 230 (15), 187 (70), 186 (100), 172 (40), 158 (44). IR (KBr) 1711 (CO). Anal. calcd for $C_{20}H_{23}N_5O$: C, 68.75; H, 6.63; N, 20.04. Found: C, 68.69; H, 6.50; N, 20.28.

**4.3.5. 3-(1*H*-1,2,3-benzotriazol-1-yl)-2-(dimethylamino)-3-hexyl-2,3-dihydro-1*H*-isoindol-1-one (18e).** Mp 103–104°C; $^1H$ NMR $\delta$ 0.78–0.85 (m, 3H), 0.88–1.03 (m, 1H), 1.13–1.29 (m, 5H), 1.33–1.43 (m, 2H), 2.49 (br. s, 6H, $NMe_2$), 3.02–3.13 (m, 1H), 3.15–3.25 (m, 1H), 6.02 (d, *J*=8.5 Hz, 1H, $H_{arom}$), 7.04–7.10 (m, 1H, $H_{arom}$), 7.20–7.24 (m, 2H, $H_{arom}$), 7.55–7.66 (m, 2H, $H_{arom}$), 7.96–8.04 (m, 2H, $H_{arom}$); $^{13}C$ NMR *C* 165.9 (CO), 146.4, 141.6, 131.7, 131.4, 83.0, *CH* 133.2, 130.6, 127.6, 124.0, 123.8, 122.9, 120.3, 110.8, $CH_2$ 33.9, 31.7, 29.2, 23.5, 22.7, $CH_3$ 44.5, 14.1. *m/z* (%): 337 ($M^+$, 100), 348 (17), 290 (22), 264 (22), 259 (30), 234 (50), 221 (47), 220 (54), 216 (40), 193 (32). IR (KBr) 1713 (CO). Anal. calcd for $C_{22}H_{27}N_5O$: C, 70.00; H, 7.21; N, 18.55. Found: C, 69.87; H, 7.34; N, 18.59.

**4.3.6. 3-(1*H*-1,2,3-benzotriazol-1-yl)-3-benzyl-2-(dimethylamino)-2,3-dihydro-1*H*-isoindol-1-one (18f).** Mp 163–164°C; $^1H$ NMR $\delta$ 2.68 (s, 6H, $NMe_2$), 3.96 (d, *J*=14.3 Hz, 1H, $CH_2Ph$), 5.28 (d, *J*=14.3 Hz, 1H, $CH_2Ph$), 5.89 (d, *J*=8.5 Hz, 1H, $H_{arom}$), 6.88 (d, *J*=7.7 Hz, 1H, $H_{arom}$), 7.21 (t, *J*=7.7 Hz, 1H, $H_{arom}$), 7.26–7.37 (m, 5H, Ph), 7.41 (t, *J*=7.8 Hz, 1H, $H_{arom}$), 7.62 (t, *J*=7.6 Hz, 1H, $H_{arom}$), 7.82 (t, *J*=7.4 Hz, 1H, $H_{arom}$), 8.13 (d, *J*=7.4 Hz, 1H, $H_{arom}$), 8.23 (d, *J*=8.5 Hz, 1H, $H_{arom}$); $^{13}C$ NMR *C* 165.5 (CO), 146.6, 140.3, 133.9, 132.0, 82.7, 68.5, *CH* 132.2, 131.6, 130.9, 128.1, 127.7, 127.4, 125.3, 124.2, 123.7, 120.3, 111.0, $CH_2$ 41.2, $CH_3$ 44.9, 14.0. *m/z* (%): 383 ($M^+$, 3), 264 (31), 221 (72), 220 (100), 193 (25), 165 (24). IR (KBr) 1717 (CO). Anal. calcd for $C_{23}H_{21}N_5O$: C, 72.04; H, 5.52; N, 18.26. Found: C, 72.16; H, 5.39; N, 18.20.

### 4.4. General procedure for the C(3)-deprotection of phthalimidines 18a–f

Compounds **18a–f** were deprotected following the same procedure previously described for the reduction of **9** but were purified by chromatography on $SiO_2$ using acetone/hexane (40:60) as eluent.

**4.4.1. 3-Butyl-2-(dimethylamino)-2,3-dihydro-1*H*-isoindol-1-one (6d).** Oil; $^1H$ NMR $\delta$ 0.83 (t, *J*=7.2 Hz, 3H), 0.96–1.07 (m, 1H), 1.15–1.32 (m, 3H), 1.81–1.94 (m, 1H), 1.96–2.07 (m, 1H), 2.96 (s, 6H, $NMe_2$), 4.43 (dd, *J*=5.8, 4.1 Hz, 1H, NCHAr), 7.31–7.43 (m, 2H, $H_{arom}$), 7.49 (dt, *J*=7.7, 1.4 Hz, 1H, $H_{arom}$), 7.75 (d, *J*=7.4 Hz, 1H, $H_{arom}$); $^{13}C$ NMR *C* 167.6 (CO), 144.1, 132.3, *CH* 131.4, 127.9, 123.1, 122.3, 61.0, $CH_2$ 30.5, 25.7, 22.8, $CH_3$ 44.1, 13.9. *m/z* (%): 232 ($M^+$, 28), 190 (100), 146 (89), 132 (48). IR (KBr) 1697 (CO). Anal. calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found: C, 72.60; H, 8.39; N, 12.11.

**4.4.2. 2-(Dimethylamino)-3-hexyl-2,3-dihydro-1*H*-isoindol-1-one (6e).** Oil; $^1H$ NMR $\delta$ 0.83 (t, *J*=6.9 Hz, 3H), 0.91–1.10 (m, 1H), 1.14–1.33 (m, 7H), 2.97 (s, 6H, $NMe_2$), 4.43 (dd, *J*=6.0, 4.0 Hz, 1H, NCHAr), 7.31–7.44 (m, 2H, $H_{arom}$), 7.49 (dt, *J*=7.4, 1.4 Hz, 1H, $H_{arom}$), 7.75 (d, *J*=7.4 Hz, 1H, $H_{arom}$); $^{13}C$ NMR *C* 167.5 (CO), 144.1, 132.4, *CH* 131.4, 127.8, 123.1, 122.3, 61.0, $CH_2$ 31.6, 30.8, 29.4, 23.5, 22.5, $CH_3$ 44.1, 14.0. *m/z* (%): 260 ($M^+$, 31), 218 (98), 146 (100), 132 (54). IR (KBr) 1699 (CO). Anal. calcd for $C_{16}H_{24}N_2O$: C, 73.81; H, 9.29; N, 10.76. Found: C, 73.69; H, 9.43; N, 10.38.

**4.4.3. 3-Benzyl-2-(dimethylamino)-2,3-dihydro-1*H*-isoindol-1-one (6f).** Mp 132–133°C; $^1H$ NMR $\delta$ 2.49 (dd, *J*=13.1, 10.2 Hz, 1H, $CH_2Ph$), 3.02 (s, 6H, $NMe_2$), 3.75 (dd, *J*=13.1, 4.1 Hz, 1H, $CH_2Ph$), 4.59 (dd, *J*=10.2, 4.1 Hz, 1H, NCHAr), 6.55 (d, *J*=7.7 Hz, 1H, $H_{arom}$), 7.15–7.20 (m, 2H, $H_{arom}$), 7.22–7.37 (m, 5H, Ph), 7.73 (d, *J*=7.4 Hz, 1H, $H_{arom}$); $^{13}C$ NMR *C* 166.9 (CO), 143.5, 137.0, 131.9, *CH* 130.9, 129.6, 128.4, 127.9, 126.8, 123.1, 122.9, 62.3, $CH_2$ 38.4, $CH_3$ 44.5. *m/z* (%): 266 ($M^+$, 35), 224 (46), 175 (100), 132 (90). IR (KBr) 1695 (CO). Anal. calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.74; H, 6.69; N, 10.64.

### 4.5. General procedure for the *N*-deprotection of phthalimidines 6a–f

Hydrazides **6a–f** (2 mmol) and zinc dust (2.6 g, 40 mmol) were stirred in glacial acetic acid (100 ml) under reflux until no starting material could be detected (TLC control, usually 24–36 h). The cold reaction mixture was filtered, evaporated, poured into aqueous $Na_2CO_3$ (5% solution, 50 ml) then extracted with $CH_2Cl_2$ (3×100 ml). The combined organic layers were washed with water, dried over $Na_2SO_4$ and evaporated to afford the crude phthalimidines, which were finally purified by chromatography on $SiO_2$ using acetone/hexane (70:30) as eluent.

**4.5.1. 3-Methyl-2,3-dihydro-1*H*-isoindol-1-one (5a).** Mp 115–116°C (lit.[16a] 115°C); $^1H$ NMR $\delta$ 1.49 (t, *J*=6.9 Hz, 3H, Me), 4.68 (q, *J*=6.9 Hz, 1H, NCHAr), 7.36–7.47 (m, 2H, $H_{arom}$), 7.53 (dt, *J*=7.4, 1.1 Hz, 1H, $H_{arom}$), 7.82 (d, *J*=7.4 Hz, 1H, $H_{arom}$), 8.54 (br. s, 1H, NH); $^{13}C$ NMR *C* 171.4 (CO), 149.0, 131.9, *CH* 131.8, 128.0, 123.5, 122.2, 52.8, $CH_3$ 13.9. *m/z* (%): 147 ($M^+$, 85), 132 (100). IR (KBr) 1658 (CO), 3224 (NH).

**4.5.2. 3-Ethyl-2,3-dihydro-1*H*-isoindol-1-one (5b).** Mp 104–105°C (lit.[26] 105°C); $^1H$ NMR $\delta$ 0.94 (t, *J*=6.9 Hz, 3H, Me), 1.63–1.73 (m, 1H), 1.94–2.07 (m, 1H), 4.59 (dd, *J*=6.9, 4.7 Hz, 1H, NCHAr), 7.39–7.45 (m, 2H, $H_{arom}$), 7.52 (dt, *J*=7.4, 1.1 Hz, 1H, $H_{arom}$), 7.83 (d, *J*=7.4 Hz, 1H, $H_{arom}$), 8.48 (br. s, 1H, NH); $^{13}C$ NMR *C* 171.5 (CO), 147.4, 132.2, *CH* 131.6, 127.9, 123.5, 122.3, 58.3, $CH_2$ 27.4, $CH_3$ 9.6. *m/z* (%): 161 ($M^+$, 19), 132 (100). IR (KBr) 1658 (CO), 1692, 3202 (NH).

**4.5.3. 3-Propyl-2,3-dihydro-1*H*-isoindol-1-one (5c).** Mp 137–138°C (lit.[27] 135–136°C); $^1H$ NMR $\delta$ 0.94 (t, *J*=7.3 Hz, 3H, Me), 1.33–1.68 (m, 3H), 1.86–1.97 (m, 1H), 4.62 (dd, *J*=7.4, 4.4 Hz, 1H, NCHAr), 7.36–7.44 (m, 2H, $H_{arom}$), 7.50 (dt, *J*=7.4, 1.1 Hz, 1H, $H_{arom}$), 7.83 (d, *J*=7.4 Hz, 1H, $H_{arom}$), 8.80 (br. s, 1H, NH); $^{13}C$ NMR *C* 171.3 (CO), 147.8, 132.0, *CH* 131.5, 127.8, 123.6, 122.3,

57.0, $CH_2$ 36.8, 19.0, $CH_3$ 14.1. *m/z* (%): 175 ($M^+$, 17), 132 (100). IR (KBr) 1681 (CO), 3194 (NH).

**4.5.4. 3-Butyl-2,3-dihydro-1*H*-isoindol-1-one (5d).** Mp 88–89°C (lit.[12b] 85–86°C); $^1$H NMR $\delta$ 1.06 (t, $J$=7.0 Hz, 3H, Me), 1.38–1.72 (m, 4H), 1.75–1.91 (m, 1H), 2.03–2.22 (m, 1H), 4.81 (dd, $J$=7.1, 5.2 Hz, 1H, NCHAr), 7.56–7.67 (m, 2H, $H_{arom}$), 7.69–7.77 (m, 1H, $H_{arom}$), 8.03 (d, $J$=7.4 Hz, 1H, $H_{arom}$), 8.33 (br. s, 1H, NH); $^{13}$C NMR *C* 171.4 (CO), 147.9, 132.0, *CH* 131.7, 128.0, 123.7, 122.4, 57.1, $CH_2$ 34.2, 27.6, 22.6, $CH_3$ 13.9. *m/z* (%): 189 ($M^+$, 14), 132 (100). IR (KBr) 1687 (CO), 3194 (NH).

**4.5.5. 3-Hexyl-2,3-dihydro-1*H*-isoindol-1-one (5e).** Mp 84–85°C; $^1$H NMR $\delta$ 0.83 (t, $J$=6.9 Hz, 3H, Me), 1.18–1.51 (m, 7H), 1.57–1.68 (m, 1H), 1.87–1.99 (m, 1H), 4.60 (dd, $J$=7.4, 4.7 Hz, 1H, NCHAr), 7.38–7.46 (m, 2H, $H_{arom}$), 7.52 (dt, $J$=7.4, 1.1 Hz, 1H, $H_{arom}$), 7.82 (d, $J$=7.4 Hz, 1H, $H_{arom}$), 8.22 (br. s, 1H, NH); $^{13}$C NMR *C* 171.3 (CO), 147.8, 132.0, *CH* 131.5, 127.8, 123.6, 122.3, 57.2, $CH_2$ 34.6, 31.6, 29.2, 25.5, 22.6, $CH_3$ 14.1. *m/z* (%): 217 ($M^+$, 16), 132 (100). IR (KBr) 1686 (CO), 3192 (NH).). Anal. calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.64; H, 8.85; N, 6.31.

**4.5.6. 3-Benzyl-2,3-dihydro-1*H*-isoindol-1-one (5f).** Mp 140–141°C (lit.[27] 135–136°C); $^1$H NMR $\delta$ 2.91 (dd, $J$=13.8, 8.4 Hz, 1H, $CH_2Ph$), 3.16 (dd, $J$=13.8, 5.7 Hz, 1H, $CH_2Ph$), 4.81 (dd, $J$=8.4, 5.7 Hz, 1H, NCHAr), 7.17–7.37 (m, 7H, NH+$H_{arom}$), 7.42–7.56 (m, 2H, $H_{arom}$), 7.83 (d, $J$=7.1 Hz, 1H, $H_{arom}$); $^{13}$C NMR *C* 170.2 (CO), 146.9, 138.8, 132.1, *CH* 131.6, 129.3, 128.7, 128.3, 127.1, 123.8, 122.8, 58.0, $CH_2$ 41.2. *m/z* (%): 223 ($M^+$, 6), 132 (100). IR (KBr) 1683 (CO), 3193 (NH).

## Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Degussa AG, BASF AG, the former Hoechst AG, and Bayer AG for the donation of chemicals.

## References

1. Polniaszek, R. P.; Belmont, S. E.; Alvarez, R. *J. Org. Chem.* **1990**, *55*, 215–223.
2. For a review about α-amino radicals see: Renaud, P.; Giraud, L. *Synthesis* **1996**, 913–926.
3. Reviews: (a) Seebach, D.; Enders, D. *Angew. Chem.* **1975**, *87* (1975), 1–18 (*Angew. Chem., Int. Ed. Engl* **1975**, *14*, 15–32). (b) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275–316. (c) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471–523. (d) Gawley, R. E.; Rein, K. In *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; pp 459–485. (e) Meyers, A. I. *Tetrahedron* **1992**, *48*, 2589–2612. (f) Beak, P.; Basee, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552–560.
4. (a) Corey, E. J. *Pure Appl. Chem.* **1967**, *14*, 19–37. (b) Seebach, D. *Synthesis* **1969**, 17–36. (c) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147–155. (d) Seebach, D. *Angew. Chem.* **1979**, *91*, 259–278 (*Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 239–258).
5. Gawley, R. E.; Chemburkar, S. R.; Smith, A. L.; Anklekar, T. V. *J. Org. Chem.* **1988**, *53*, 5381–5383.
6. (a) Beeley, L. J.; Rockell, C. J. M. *Tetrahedron Lett.* **1990**, *31*, 417–420. (b) Meyers, A. I.; Santiago, B. *Tetrahedron Lett.* **1995**, *36*, 5877–5880.
7. (a) Beak, P.; Kerrick, S. T.; Gallagher, D. J. *J. Am. Chem. Soc.* **1993**, *115*, 10628–10636. (b) Couture, A.; Deniau, E.; Ionescu, D.; Grandclaudon, P. *Tetrahedron Lett.* **1998**, *39*, 2319–2320. (c) Luzzio, F. A.; Zacherl, D. P. *Tetrahedron Lett.* **1998**, *39*, 2285–2238.
8. (a) Kundu, N. G.; Khan, M. W.; Mukhopadhyay, R. *Tetrahedron* **1999**, *55*, 12361–12376 (and references cited). (b) Luzzio, A. F.; Zacherl, D. P.; Figg, W. D. *Tetrahedron Lett.* **1999**, *40*, 2087–2090 (and references cited). (c) Cai, Y.; Fredenhagen, A.; Hug, P.; Meyer, T.; Petre, H. *J. Antibiot. Chem.* **1996**, *49*, 519–526. (d) Campello, M. J.; Castedo, L.; Domínguez, D.; Rodriguez de Lera, A.; Saá, J. M.; Suau, R.; Tojo, E.; Vidal, M. C. *Tetrahedron Lett.* **1984**, *25*, 5933–5936. (e) Valencia, E.; Fajardo, V.; Freyer, A. J.; Shamma, M. *Tetrahedron Lett.* **1985**, *26*, 993–996. (f) Chang, Z-L.; Zhu, D-Y. In *The Alkaloids*; Academic: New York, 1987; pp 29–65.
9. (a) Belliotti, T. R.; Brink, W. A.; Kesten, S. R.; Rubin, J. R.; Wustrow, D. J.; Zoski, K. T.; Whetzel, S. Z.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1499–1502. (b) Takahashi, I.; Hirano, E.; Kawakami, T.; Kitajima, H. *Heterocycles* **1996**, *43*, 2343–2346. (c) Takahashi, I.; Kawakami, T.; Hirano, E.; Yokota, H.; Kitajima, H. *Synlett* **1996**, 353–355.
10. Zhuang, Z.-P.; Kung, M.-P.; Mu, M.; Kung, H. F. *J. Med. Chem.* **1998**, *41*, 157–166.
11. Wood, J. L.; Petsch, D. T.; Stoltz, B. M.; Hawkins, E. M.; Elbaum, D.; Stover, D. R. *Synthesis* **1999**, 1529–1533.
12. (a) Helberger, J. H.; Rebay, A. V.; Hevér, D. B. *Liebigs Ann. Chem.* **1938**, 197–212. (b) Noguchi, T.; Kawanami, M. *J. Pharm. Soc. Jpn* **1937**, *57*, 196–208. (c) Tikk, I.; Deak, G.; Tamas, J. *Acta. Chim. Hung.* **1988**, *125*, 289–294.
13. (a) Caronna, G.; Palazzo, S. *Gazz. Chim. Ital.* **1953**, *83*, 308–314. (b) Pfeiffer, P.; Jalnsch, E. *J. Prakt. Chem.* **1941**, *159*, 241–263. (c) Henze, H. R.; Leanza, W. J. *J. Org. Chem.* **1952**, *17*, 4–12.
14. Oppolzer, W.; Wills, M.; Kelly, M. J.; Signer, M.; Blagg, J. *Tetrahedron Lett.* **1990**, *31*, 5015–5018.
15. (a) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1999**, *40*, 141–142. (b) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1999**, *40*, 143–146.
16. (a) Helberger, J. H.; Rebay, A. V. *Liebigs Ann. Chem.* **1939**, 187–197. (b) Gabriel, S.; Giebe, G. *Chem. Ber.* **1896**, *29*, 2518–2525. (c) Rodianow, W. M.; Fedorova, A. M. *J. Am. Chem. Soc.* **1930**, *52*, 368–371. (d) Linstead, R. P.; Rowe, G. A. *J. Chem. Soc.* **1940**, 1070–1076. (e) Kreher, R. P.; Hennige, H.; Konrad, M.; Uhrig, J.; Clemens, A. *Z. Naturforsch* **1991**, *B46*, 809–828.
17. Gregory, R. M.; Grieco, P. A.; Chidambaram, V. S. *J. Org. Chem.* **1981**, *46*, 3761–3763.
18. Enders, D.; Lochtman, R.; Meiers, M.; Müller, S.; Lazny, R. *Synlett* **1998**, 1182–1184.
19. (a) Kreher, R. P.; Hennige, H.; Jelitto, F.; Preut, J. *Z. Naturforsch* **1989**, *44*, 1132–1148. (b) Norman, M. H.; Kelly, J. L.; Hollingsworth, E. B. *J. Med. Chem.* **1993**, *36*, 3417–3423. (c) Egbertson, M. S.; Bednar, B.; Bednar, R. A.; Hartman, G. D.; Gould, R. J.; Lynch, R. J.; Vassalo, L. M.;

Young, S. D. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1415–1420. (d). Taylor, E. C.; Jennings, L. D.; Mao, Z.; Hu, B.; Jun, J.-G.; Zhou, P. *J. Org. Chem.* **1997**, *62*, 5392–5403.

20. (a) Berube, D.; Lessard, J. *Can. J. Chem.* **1982**, *60*, 1127–1142. (b) Reiffen, M.; Eberlein, W.; Mueller, P.; Psiorz, M.; Noll, K.; Heider, J.; Lillie, C.; Kobinger, W.; Luger, P. *J. Med. Chem.* **1990**, *33*, 1496–1504.
21. (a) Anzini, M.; Capelli, A.; Vomero, S.; Cagnoto, A.; Skorupska, M. *J. Heterocycl. Chem.* **1992**, *29*, 1111–1115. (b) Ellis, G. P.; Rommey-Alexander, T. M. *J. Chem. Res. (M)* **1984**, *11*, 3101–3118. (c) Krepelka, J.; Vancurova, I.; Holubek, J. *Collect. Czech. Chem. Commun.* **1982**, *47*, 1252–1257.
22. Drew, H. D. K.; Hatt, H. H.; Hobart, F. A. *J. Chem. Soc.* **1937**, 33–35.
23. (a) Hugues, I.; Nolan, W. P.; Raphael, R. A. *J. Chem. Soc. Perkin Trans. 1* **1990**, *9*, 2475–2480. (b) Mamouni, A.; Pigeon, P.; Daich, A.; Decroix, B. *J. Heterocycl. Chem.* **1997**, *34*, 1495–1499.
24. (a) Katritzky, A. R.; Drewniak-Deyrup, M.; Lan, X.; Brunner, F. *J. Heterocycl. Chem.* **1989**, *26*, 829–836. (b) Katritzky, A. R.; Yang, Z.; Lam, J. N. *J. Org. Chem.* **1991**, *56*, 2143–2147. (c) Katritzky, A. R.; Yang, Z.; Lam, J. N. *J. Org. Chem.* **1991**, *56*, 6917–6923.
25. (a) Mellor, J. M.; Smith, N. M. *J. Chem. Soc. Perkin Trans. 1* **1984**, *5*, 557–560. (b) Enders, D.; Demir, A. S.; Puff, H.; Franken, S. *Tetrahedron Lett.* **1987**, *28*, 3795–3798. (c) Beaudegnies, R.; Ghosez, L. *Tetrahedron: Asymmetry* **1994**, *5*, 557–560. (d) Leblanc, Y.; Boudreault, N. *J. Org. Chem.* **1995**, *60*, 4268–4271. (e) Cueva, J. M.; Echavarren, A. M. *Synlett* **1997**, 173–174. (f) McClure, C. K.; Mishra, P. K.; Grote, C. W. *J. Org. Chem.* **1997**, *62*, 2437–2441. (g) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595–598.
26. Helberger, J. H.; Hevér, D. B. *Liebigs Ann. Chem.* **1938**, *536*, 173–182.
27. Bronberg, O. *Chem. Ber.* **1896**, *29*, 1434–1442.