Acid-Promoted Aza-Cyclization versus π-Cyclization of *N*-Acyliminium Species into Fused Pyrrolo[1,2-*a*]imidazolones and Pyrrolo[2,1-*a*]-isoquinolinones

Jean-François Fleury, Pierre Netchitaïlo, Adam Daïch*

Laboratoire de Chimie, URCOM, EA 3221, INC3M CNRS-FR 3038, UFR des Sciences et Techniques, Université du Havre, BP: 540, 25 Rue Philippe Lebon, 76058 Le Havre Cedex, France
Fax +33(2)32744391; E-mail: adam.daich@univ-lehavre.fr

Received 7 February 2011

Abstract: A new approach for the synthesis of fused imidazolones and isoquinolinones is presented. The key step of this sequence was the interception of an *N*-acyliminium species with nitrogen or π-aromatic nucleophiles under kinetic vs. thermodynamic control. In addition, in the presence of two π-aromatic nucleophiles, only the six-membered ring closure into pyrroloisoquinolinones occurred.

Key words: *N*-acyliminium, diastereoselectivity, aza-cyclization, pyrrolo[1,2-*a*]imidazolone, pyrrolo[2,1-*a*]isoquinolinone

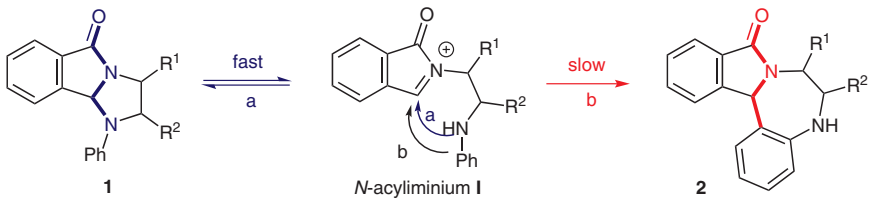
N-Acyliminium species are intermediates which are widely used in modern organic synthesis. Their importance is underlined by numerous reviews of their generation and use for the elaboration of natural and unnatural aza-heterocyclic systems with therapeutic interest.[1] If the formation of the C–C bonds by this protocol in inter- and intramolecular fashion is widely applied by the scientific community, the one which consists in the formation of the C–X linkage with X as a heteroatom (X = O, S, Se, and N) appears to be a new field of application of this chemistry.[2,3]

We have described earlier the potential for these species to intercept intramolecularly nitrogen nucleophiles in acidic media.[2] In particular, their presence with both carbon- and nitrogen-tethered nucleophiles showed the reaction operability under kinetic vs. thermodynamic control (Scheme 1). This resulted in the formation of C–N bond (**1**, reversible) or C–C bond (**2**, irreversible) depending on the reaction conditions.[3] Similar processes in oxygen series are relatively well documented to provide, in particular, asymmetric macrocyclic *N*,*O*-acetals[4] and alkaloids.[5] In both cases, Brønsted and Lewis acids were used as promoters.

Moreover, cationic cyclization using a nitrogen atom as internal nucleophile was first mentioned during the synthesis of 9*a*-phenyltetrahydroisoindolo[2,1-*a*]quinazoline-5,11-dione[6a] and ten years later for the production of diethyl tetrahydrodioxolo[4,5-*g*]pyrrolo[2,1-*b*]quinazoline-8,8-dicarboxylate.[6b] Its power was also illustrated in the total synthesis of (±)- and (–)-physostigmine,[7] (±)-glochidine, and (±)-glochidicine,[8] imidazoloindoline alkaloids,[9a] oroidin-derived alkaloids,[9b] and more recently, the bioactive enantiopure (–)-decarbamoyloxy-saxitoxin.[10] Reports on this process concern also its use to access aldose reductase inhibitors,[11] in parallel synthesis of Δ^2-2-oxopiperazines,[12] in asymmetric synthesis of Reissert compounds,[13] in synthesis of lactam-based peptidomimetics,[14] and in sterically hindered N-substituted and fused γ-lactams.[15]

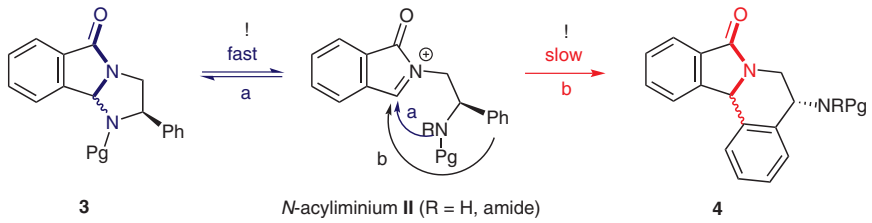
To the best of our knowledge, the use of the present application in both intramolecular and diastereoselective *N*-acyliminium-mediated cyclization represents a novel illustration of this chemistry (Scheme 2). This can result in the formation of a central five-membered ring of *N*,*N*-acetal **3** by nitrogen atom attack of the cation **II** (path a). However, when the aromatic system at the nitrogen α-position of **II** is sufficiently activated, a six-membered ring of fused isoquinoline **4** (path b) can be obtained. The cores of these tricyclic systems ars often encountered in natural products and biologically active compounds.[16]

For this purpose, the requisite α-hydroxy lactam **9** was obtained in three steps from commercially available (*R*)-phenylglycinol (**5**, Scheme 3). Protection of (*R*)-**5** with



Scheme 1 Representative kinetic vs. thermodynamic control of cationic cyclization of *N*-acyliminiums of type **I**

SYNLETT 2011, No. 13, pp 1821–1826
Advanced online publication: 14.07.2011
DOI: 10.1055/s-0030-1260949; Art ID: D04011ST



Scheme 2 Plausible kinetic vs. thermodynamic control of cationic cyclization of *N*-acyliminiums of type **II**

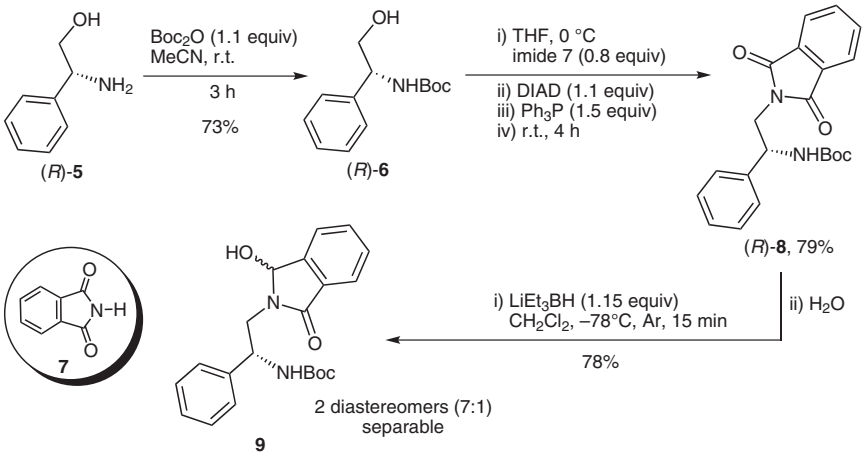
$(Boc)_2O$ provided *N*-Boc derivative (*R*)-**6** in 73% yield according to the known procedure.[17] The second step of our sequence consisted in coupling the imide **7** with *N*-Boc-(*R*)-phenylglycinol (**6**). The Mitsunobu reaction was implemented with DIAD instead of DEAD usually employed as coupling reagent by applying conditions of Martinez et al. (imide **7**, DIAD, Ph_3P, THF, 0 °C).[18] Under these conditions, the expected chiral imide **8** was isolated in 79% yield.

It has been demonstrated[1] that the reduction of one of both imide carbonyls can lead to several alcohols including the secondary α-hydroxy lactam we required as *N*-acyliminium precursor. After optimization work, the chemoselective reduction of (*R*)-**8** was performed with a slight excess of $LiEt_3BH$ (1.15 equiv) in analogy with our reports.[19] This afforded the α-hydroxy lactam **9** (78% yield) as a mixture of two diastereomers (7:1) separable by chromatography (EtOAc–cyclohexane = 2:3).

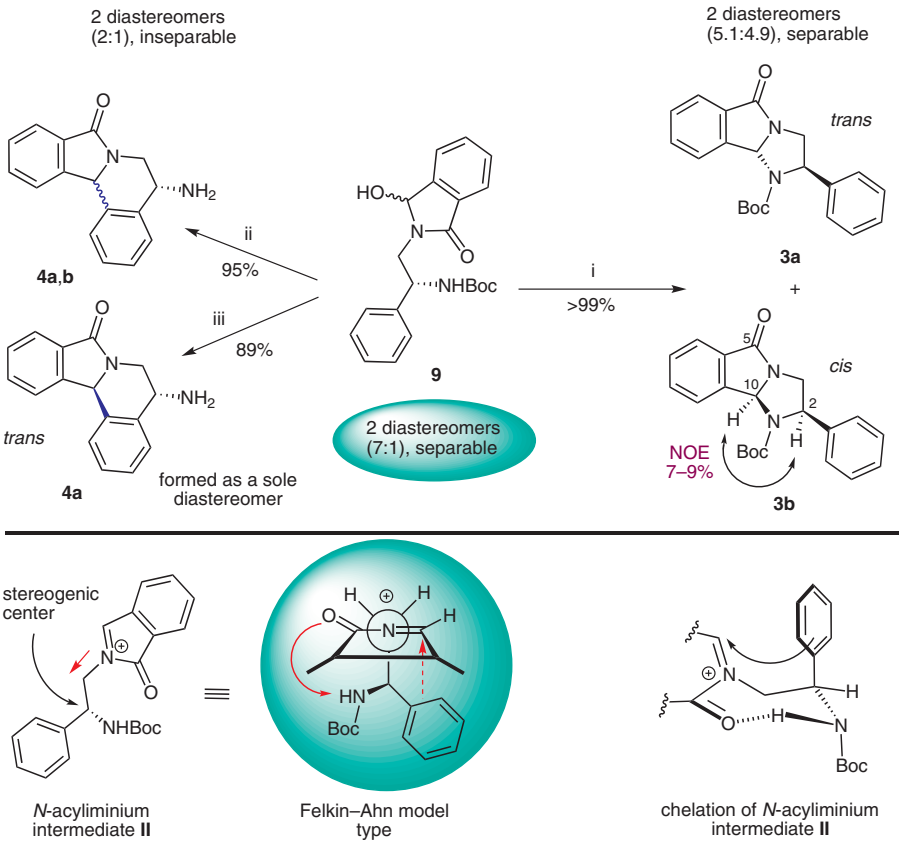
According to previous reports[1] demonstrating that Brønsted and Lewis acids are good catalysts for various amidoalkylations, we thought to use PTSA, TFA, and $BF_3{\cdot}OEt_2$ for the intramolecular π-cyclization and/or α-hetero-amidoalkylation in order to measure the impact of these acids on the ring-closure step. Thus, treatment of **9** (two diastereomers), as a precursor of stable cation **II** (Scheme 2; Scheme 4), with PTSA (10 mol%) in dry CH_2Cl_2 at reflux for 30 minutes afforded *N*-Boc-imidazoisoindolone diastereomers **3a** and **3b** in 5.1:4.9 ratio.[20] This mixture, which resulted from exclusive α-aza-amidoalkylation, was obtained in quantitative yield and separated simply by silica gel chromatography. The stereochemical relationship in **3a** and **3b** was established by using selective NOE difference measurements. In the major product **3b** a strong NOE effect was observed confirming the *cis* orientation of H_2 and H_{10} (Scheme 4).[21] This showed also that the stereochemical outcome during the formation of the major isomer is similar to that we reported earlier in the oxygen series.[22]

Taking into account that TFA is a standard deprotecting agent for the Boc group, we decided to use it for the cyclization process, hoping to be able to promote both the cyclization reaction and the amine deprotection at the same time. Thus, α-hydroxy lactam **9** (each isomer or both diastereomers) upon treatment with neat TFA for 30 minutes at room temperature followed by alkaline hydrolysis gave isoquinolines **4a** and **4b**. These tricyclic systems were isolated as free amines in an inseparable 2:1 ratio and excellent 95% yield. Finally, by using an excess of $BF_3{\cdot}OEt_2$ according to the standard protocol (2.5 equiv $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C), after one hour of the reaction at room temperature we also observed the formation of the unique isoquinoline system present as only one diastereomer **4a** accompanied by the deprotection of the amine function. Interestingly, the latter fact has rarely been observed under $BF_3{\cdot}OEt_2$ influence and consequently little reported in the literature.

The formation of both isomers **4a**,**b** can be explained by the π-aromatic attack on either face of the cation **II** formed in acid medium by invoking a Felkin–Ahn-type[23] model (Scheme 4). The plausible chelation in the cation **II** is probably at the origin of the diastereoselectivity we observed (**4a** as major isomer or exclusive isomer). Furthermore, the formation of the imidazoisoindolones **3** and isoquinolines **4** seems to occur by kinetic versus thermo-

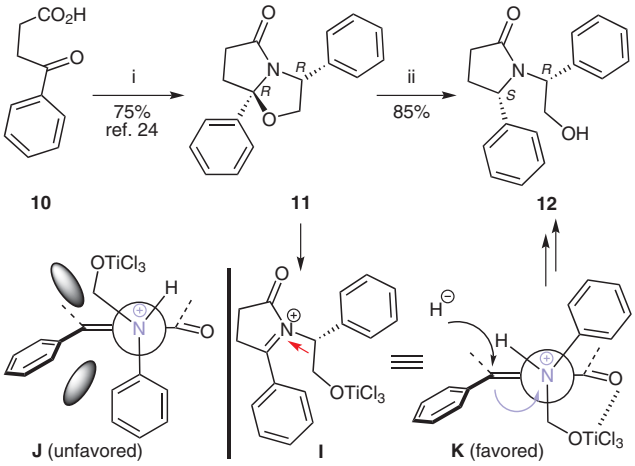


Scheme 3 Sequence leading to the *N*-acyliminium precursor **9**



Scheme 4 Cyclization reaction. *Reagents and conditions*: (i) PTSA (10 mol%), CH_2Cl_2, reflux, 30 min; (ii) (a) TFA, r.t., 30 min; (b) aq $NaHCO_3$, CH_2Cl_2; (iii) (a) $BF_3{\cdot}OEt_2$ (2.5 equiv), CH_2Cl_2, 0 °C; (b) r.t., 1 h.

dynamic control using the formal species **II** as intermediate. This was confirmed when **3a**,**b** as a mixture of two diastereomers was treated with neat TFA under conditions ii as in Scheme 4 but for a longer time (4 h). Under these conditions, imidazoisoindolones **3a**,**b** generate the cationic platform **II**, and the isoquinolines **4a**,**b** were again obtained in 90% yield and comparable ratio of 2.5:1.5 with the same stereodistribution as before.



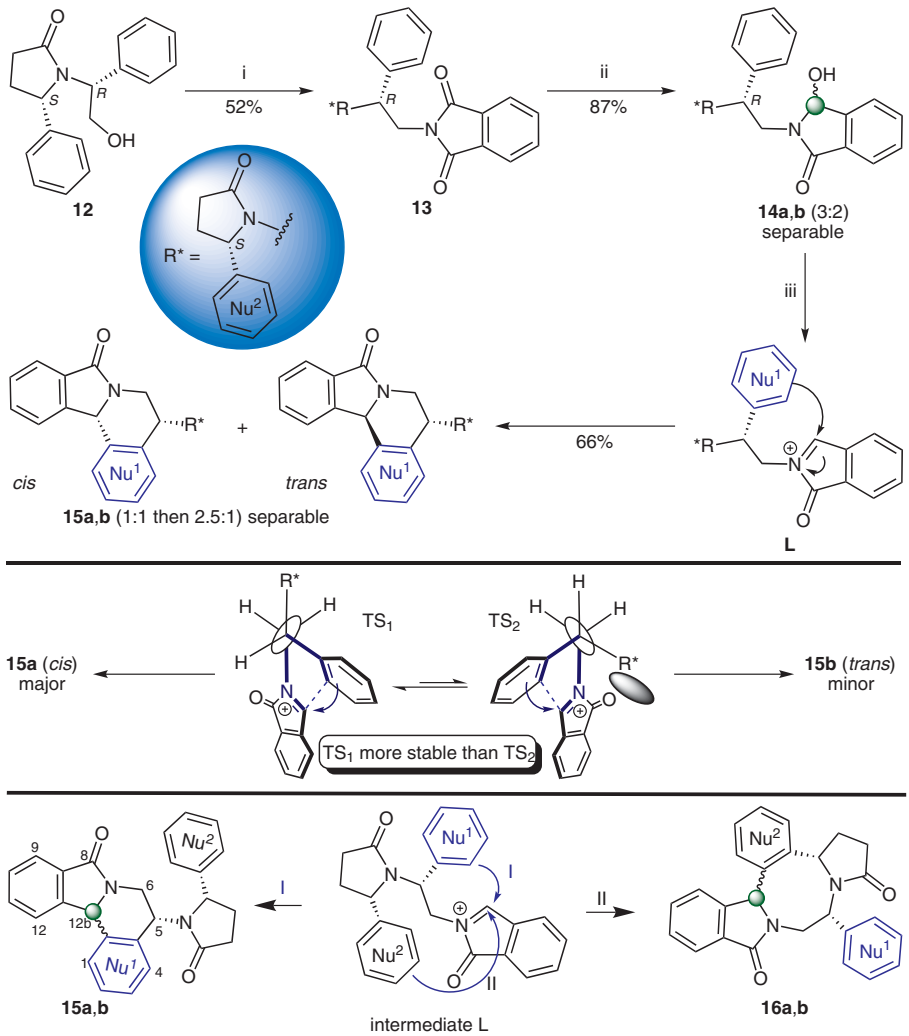
Scheme 5 Synthesis of alcohol **12**. *Reagents and conditions*: (i) (*R*)-**5** (1 equiv), toluene, DS, reflux, 12 h; (ii) (1) Et_3SiH (3.2 equiv), CH_2Cl_2, –78 °C; (2) $TiCl_4$ (2 equiv), –78 °C, 1 h 30; (3) r.t., 12 h; (4) sat. aq NH_4Cl, r.t., 30 min.

In another approach, the competing electrophilicity of the *N*-acyliminium species towards π-aromatic systems was again explored. Herein, the principal objective was to access the isoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one skeleton starting from known keto acid **10** (Scheme 5) but substituted at the amine group at C_5, hoping to be able to separate the diastereomers.

As outlined in Scheme 5, the first key substrate (*S*,*R*)-**12** was reached in two steps. Thus, the known enantiopure oxazolidine product (*R*,*R*)-**11**, prepared by Meyers' method in 75% yield,[24] in the presence of $TiCl_4$ and Et_3SiH in dry CH_2Cl_2 provided the expected amido alcohol (*S*,*R*)-**12** in 85% yield and high diastereoselectivity since only one diastereomer was isolated. The usual rationalization[25] invokes initial formation of the intermediate **I**. Further, the attack of the hydride occurs at the cationic position on the upper side of the Felkin–Ahn model such as in the intermediate **K** which would be favorably formed by a chelation process in preference to cation **J**.

Amido alcohol **12** was then engaged in the Mitsonubu reaction according to the protocol outlined above for the transformation of (*R*)-**6** into **8** (Scheme 3). Under these conditions, the enantiopure imide **13** was isolated in 52% yield after purification by chromatography (Scheme 6).

The imide **13** was then reduced chemoselectively as above and led, after basic hydrolysis, to pure hydroxy lactam **14** in 87% yield. This product, obtained as a mixture of two separable diastereomers **14a**,**b** (3:2 ratio), results from the



Scheme 6 *Reagents and conditions*: (i) (1) phthalimide (**7**, 1.1 equiv), THF, (2) DIAD (1.2 equiv), 0 °C; (3) Ph_3P (1.5 equiv), 0 °C; (4) r.t., 2 h; (ii) (1) $LiEt_3BH$ (1.15 equiv), CH_2Cl_2, –78 °C, 15 min; (2) sat. aq $NaHCO_3$, r.t.; (iii) (1) TFA, Ar, r.t., 2 h; (2) CH_2Cl_2, $NaHCO_3$.

attack of the hydride on both faces of the phthalimide nucleus. In addition, the observed relative selectivity in the reaction can be explained by the presence of a stereogenic center at the β-position of the phthalimide nucleus which directs the approach of the hydride.

Each cation precursor **14a** or **14b**, having been separated chromatographically, was alternatively subjected to the intramolecular π-cyclization under conditions outlined above (Scheme 6). This resulted in the formation of the presumably stable cation **L** which undergoes an intramolecular π-amidoarylation. Interestingly, after two hours of the reaction, in both cases approximately 66% of diastereomeric mixture of products **15a**,**b** with very poor diastereoselectivity (1:1 ratio) was isolated. This shows that exclusively the expected six-membered-ring pathway is effective according to the Baldwin rules (path I, Scheme 6).[26] Similarly, starting from crude hydroxy lactam **14a**,**b** (3:2 ratio) without purification and separation, the reaction likewise led to the same mixture in comparable yield and stereochemical distribution.

Importantly, it was found that the π-cyclization of **14a** and/or **14b** into **15a**,**b** could be improved in some aspects, when the reaction was refluxed for two hours in the same solvent with other parameters unchanged. The results show that the stereochemical distribution of products **15a**,**b**,[27] separable by chromatography, was now of 2.5:1 ratio in favor of the diastereomer **15a** which could be considered as a thermodynamically favored isomer. Nevertheless, in spite of this success, the reaction yield (48% of the crude reaction products) was lower than the one obtained above (66%), and the reaction was associated with decomposition of the reactants in acid medium. Since the configuration of both compounds could not be determined by X-ray crystallography analysis due to the difficulties encountered during recrystallization attempts, it was tentatively assigned on the basis of studies given by the Speckamp group and initiated by the Maryanoff et al. on pyrrolo[2,1-*a*]isoquinolinones substituted with alkyl or aryl groups at their C_6-position.[28] In these cases, they observed an isomeric ratio for 6α/6β ranging from 55.5:34.5 up to 93:7 depending on the nature of the substituent. The stereochemical outcome of the reaction has been interpreted in terms of the steric requirements of the substituent at C_6 favoring a chairlike transition state as the cyclization intermediate. In this case, the more stable con-

formation in $\mathbf{TS_1}$ compared with $\mathbf{TS_2}$ would lead to *cis*-**15a** as the major product (Scheme 6).[29]

In conclusion, we have developed a short and effective synthesis of enantiopure fused pyrroloimidazolones **3** and pyrroloisoquinolinones **4** based on kinetic vs. thermodynamic control of an intramolecular electrophilic cyclization when both nitrogen and π-aromatic nucleophiles are present in an *N*-acyliminium precursor. The reaction proceeds with good to very high yields and moderate diastereoselectivity. Moreover, with two π-aromatic nucleophiles, the *N*-acyliminium cyclization onto chiral substituted isoindoloisoquinolinones **15** related to **4** occurs with acceptable yields and low stereochemical distribution. Only a six-membered-ring pathway as opposed to an eight-membered occurred during these transformations. In this case the diastereomeric ratio could be interestingly modified (up to 2.5:1 ≈ 71.5:28.5 in non-optimized conditions) by varying the reaction temperature without changing other parameters.

These simple modular approaches are currently under investigation in our group to access various scaffolds analogous to natural products.

Acknowledgment

We are grateful to Le Havre University for material support (J.F.F.) and to Dawn Hallidy for proofreading the text.

References and Notes

(1) For important reviews in this area, see: (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (b) Maryanoff, B. E.; Zhang, H. C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.

(2) For aza-cyclization, see: (a) Fogain-Ninkam, A.; Daïch, A.; Netchitaïlo, P.; Decroix, B. *Eur. J. Org. Chem.* **2003**, 427. (b) Oukli, N.; Comesse, S.; Chafi, N.; Oulyadi, H.; Daïch, A. *Tetrahedron Lett.* **2009**, *50*, 1459.

(3) Cul, A.; Daïch, A.; Decroix, B.; Sanz, G.; Van Hijfte, L. *Tetrahedron* **2004**, *60*, 11029.

(4) For oxa-cyclization, see: (a) Mamouni, A.; Daïch, A.; Marchalín, Š.; Decroix, B. *Heterocycles* **2001**, *54*, 275. (b) Sikoraiova, J.; Chihab-Eddine, A.; Marchalín, Š.; Daïch, A. *J. Heterocycl. Chem.* **2002**, *39*, 383. (c) Pesquet, A.; Van Hijfte, L.; Daïch, A. *ARKIVOC* **2010**, *(viii)*, 27.

(5) See, for example: Allin, S. M.; Gaskell, S. N.; Elsegood, M. R. J.; Martin, W. P. *J. Org. Chem.* **2008**, *73*, 6448.

(6) (a) Aeberli, P.; Houlihan, W. J. *J. Org. Chem.* **1968**, *33*, 2402. (b) Massa, S.; De Martino, G. *Farmaco* **1978**, *33*, 271.

(7) (a) Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 2399. (b) Marino, J. P.; Bogdan, S.; Kimura, K. *J. Am. Chem. Soc.* **1992**, *114*, 5566. (c) El Azab, A. S.; Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 2757.

(8) Lee, Y. S.; Kim, S. H.; Jung, S. H.; Lee, S. J.; Park, H. *Heterocycles* **1994**, *37*, 303.

(9) (a) Barbosa, Y. A. O.; Hart, D. J.; Magomedov, N. A. *Tetrahedron* **2006**, *62*, 8748. (b) Dransfield, P. J.; Dilley, A. S.; Wang, S.; Romo, D. *Tetrahedron* **2006**, *62*, 5223.

(10) Iwamoto, O.; Koshino, H.; Hashizume, D.; Nagasawa, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 8625.

(11) (a) Yamagishi, M.; Yamada, Y.; Ozaki, K.; Date, T.; Okamura, K.; Suzuki, M.; Matsumoto, K. *J. Org. Chem.* **1992**, *57*, 1568. (b) Yamagishi, M.; Yamada, Y.; Ozaki, K.; Asao, M.; Shimizu, R.; Suzuki, M.; Matsumoto, M.; Matsuoka, Y.; Matsumoto, K. *J. Med. Chem.* **1992**, *35*, 2085.

(12) Lee, S.-C.; Park, S. B. *J. Comb. Chem.* **2007**, *9*, 828.

(13) (a) Surygina, O.; Ehwald, M.; Liebscher, J. *Tetrahedron Lett.* **2000**, *41*, 5479. (b) Sieck, O.; Schaller, S.; Grimme, S.; Liebscher, J. *Synlett* **2003**, 337.

(14) (a) Le Quement, S. T.; Nielsen, T. E.; Meldal, M. *J. Comb. Chem.* **2007**, *9*, 1060. (b) Min, B. J.; Gu, X.; Yamamoto, T.; Petrov, R. R.; Qu, H.; Lee, Y. S.; Hruby, V. J. *Tetrahedron Lett.* **2008**, *49*, 2316; and references cited therein.

(15) (a) Sannigrahi, M.; Pinto, P.; Chan, T. M.; Shih, N.-Y.; Njoroge, F. G. *Tetrahedron Lett.* **2006**, *47*, 4877. (b) Cayley, A. N.; Gallagher, K. A.; Ménard-Moyon, C.; Schmidt, J. P.; Diorazio, L. J.; Taylor, R. J. K. *Synthesis* **2008**, 3846.

(16) Moreau, A.; Couture, A.; Deniau, E.; Grandclaudon, P. *Eur. J. Org. Chem.* **2005**, 3437; and references cited therein.

(17) Lewanowicz, A.; Lipinski, J.; Siedlecka, R.; Skarzewski, J.; Baert, F. *Tetrahedron* **1998**, *54*, 6571.

(18) Martinez, E. J.; Corey, E. J. *Org. Lett.* **2000**, *2*, 993.

(19) Pin, F.; Comesse, S.; Garrigues, B.; Marchalín, Š.; Daïch, A. *J. Org. Chem.* **2007**, *72*, 1181.

(20) The ratio of both diastereomers **3a**,**b** considered as kinetic products was estimated by ^{1}H NMR spectroscopy and is different from that of their amidal congeners **9** in a 7:1 ratio.

(21) **Data for Compound 3b**
Isolated in 51% yield as a white solid (EtOAc–cyclohexane = 1:4); mp 136 °C; $[\alpha]_D$ –20.9 (*c* 0.81×10^{-3}, CH_2Cl_2). IR (KBr): ν_{max} = 3019, 1687 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (s, 9 H), 3.33 (dd, 1 H, *J* = 12.0, 8.0 Hz), 4.64 (dd, 1 H, *J* = 12.3, 7.6 Hz), 4.80 (t, 1 H, *J* = 7.8 Hz), 7.25–7.38 (m, 5 H_{Ar}), 7.51 (t, 1 H_{Ar}, *J* = 7.2 Hz), 7.58 (t, 1 H_{Ar}, *J* = 7.2 Hz), 7.80 (d, 1 H_{Ar}, *J* = 7.2 Hz), 8.16 (d, 1 H_{Ar}, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.1, 51.7, 64.7, 75.9, 81.0, 122.8, 125.4, 126.8, 127.7, 128.9, 131.8, 132.7, 144.3, 153.6, 179.9. MS (EI): *m/z* = 350 [M$^+$]. Anal. Calcd (%) for $C_{21}H_{22}N_2O_3$ (350.16): C, 71.98; H, 6.33; N, 7.99. Found: C, 71.77; H, 6.18; N, 7.76.

(22) Sikoraiova, J.; Daïch, A.; Marchalín, Š.; Decroix, B. *Tetrahedron Lett.* **2002**, *43*, 4747.

(23) (a) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem.* **1991**, *56*, 4868. (b) Chihab-Eddine, A.; Daïch, A.; Jilale, A.; Decroix, B. *Tetrahedron Lett.* **2001**, *42*, 573.

(24) (a) Meyers, A. I.; Burgess, L. E. *J. Org. Chem.* **1991**, *56*, 2294. (b) Burgess, L. E.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 1656; and references cited therein.

(25) (a) Allin, S. M.; Duffy, L. J.; Page, P. C. B.; McKee, V.; Edgar, M.; McKenzie, M. J.; Amat, M.; Bassas, O.; Santos, M. M. M.; Bosch, J. *Tetrahedron Lett.* **2006**, *47*, 5713. (b) Amat, M.; Bassas, O.; Llor, N.; Canto, M.; Perez, M.; Molins, E.; Bosch, J. *Chem. Eur. J.* **2006**, *12*, 7872.

(26) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Baldwin, J. *Tetrahedron* **1982**, *38*, 2939.

(27) **Data for Compound 15a**
Isolated in 35% yield as an orange solid (EtOAc–cyclohexane = 2:3; R_f = 0.17); mp 171 °C; $[\alpha]_D$ –212.4 (*c* 1.45×10^{-3}, CH_2Cl_2). IR (KBr): ν_{max} = 3019, 1686 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.02–20.7 (m, 1 H), 2.35–2.56 (m, 3 H), 3.91–4.03 (m, 1 H), 4.30 (s, 2 H), 4.81 (s, 1 H), 5.59 (s, 1 H), 7.12–7.24 (m, 5 H_{Ar}), 7.30–7.33 (m, 4 H_{Ar}), 7.44–7.48 (t, 1 H_{Ar}, *J* = 6.6 Hz), 7.56 (d, 1 H_{Ar}, *J* = 6.0 Hz), 7.67 (d, 1 H_{Ar}, *J* = 7.2 Hz), 7.75 (d, 1 H_{Ar}, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.8, 31.5, 39.3, 51.6, 59.1, 66.6, 123.7, 124.2, 126.0, 126.4, 127.3 (2×), 127.6, 127.8, 128.8, 129.2, 129.6 (2×), 132.0, 132.5, 134.4, 135.0, 140.9, 145.0, 167.5, 175.7. MS (EI): *m/z* = 394 [M$^+$]. Anal. Calcd (%) for

$C_{26}H_{22}N_2O_2$ (394.48): C, 79.16; H, 5.62; N, 7.10. Found: C, 79.06; H, 5.52; N, 7.05.

Data for Compound 15b

Isolated in 31% yield as an orange solid (EtOAc–cyclohexane = 2:3; R_f = 0.11); mp 216 °C; $[\alpha]_D$ –210.9 (*c* 0.82×10^{-3}, CH_2Cl_2). IR (KBr): ν_{max} = 3019, 1676 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.50–1.57 (m, 1 H), 2.30–2.48 (m, 2 H), 2.50–2.65 (m, 1 H), 3.53 (dd, 1 H, *J* = 14.1, 3.7 Hz), 4.19 (d, 1 H, *J* = 8.0 Hz), 4.78 (dd, 1 H, *J* = 14.1 Hz), 5.54–5.56 (m, 2 H), 6.23–6.29 (m, 2 H_{Ar}), 6.56 (t, 2 H_{Ar}, *J* = 7.1 Hz), 6.71 (t, 1 H_{Ar}, *J* = 7.1 Hz), 6.84 (t, 1 H_{Ar}, *J* = 7.4 Hz), 6.98 (d, 1 H_{Ar}, *J* = 7.4 Hz), 7.13 (t, 1 H_{Ar}, *J* = 7.4 Hz), 7.46 (d, 1 H_{Ar}, *J* = 7.4 Hz), 7.55 (t, 1 H_{Ar}, *J* = 7.2 Hz), 7.63 (t, 1 H_{Ar}, *J* = 7.2 Hz), 7.81 (t, 1 H_{Ar}, *J* = 7.2 Hz), 7.95 (d, 1 H_{Ar}, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.2, 29.8, 42.1, 50.4, 58.9, 61.8, 123.4, 124.1, 125.0, 125.7 (2×), 126.7, 127.1, 127.8 (2×), 128.6, 129.0, 131.7, 132.1, 132.3, 132.9, 133.9, 141.8, 143.7, 167.9, 176.6; MS (EI): *m/z* = 394 [M^+]. Anal. Calcd (%) for $C_{26}H_{22}N_2O_2$ (394.48): C, 79.16; H, 5.62; N, 7.10. Found: C, 78.96; H, 5.50; N, 6.93.

(28) (a) See also the review in ref. 1b: (b) Maryanoff, B. E.; McComsey, D. F. *Tetrahedron Lett.* **1979**, 3797. (c) Maryanoff, B. E.; McComsey, D. F.; Duhl-Emswiler, B. A. *J. Org. Chem.* **1983**, *48*, 5062. (d) Ent, H.; de Koning, H.; Speckamp, W. N. *J. Org. Chem.* **1986**, *51*, 1687.

(29) For the stereochemical distribution, see: Katritzky, A. R.; Mehta, S.; He, H.-Y. *J. Org. Chem.* **2001**, *66*, 148.