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Stereoselective iodocyclisation of 3-acylamino-2-methylene alkanoates: a computational insight

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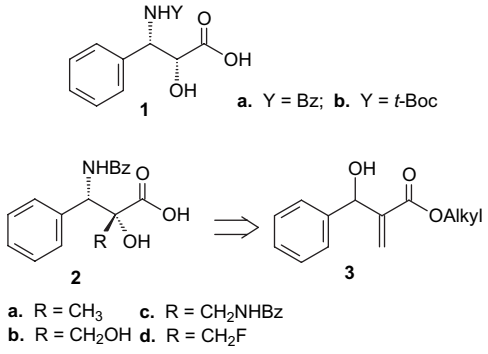
Abstract—In order to explain the high stereocontrol occurring in the iodocyclisation of 3-acylamino-2-methylenealkanoates, either the conformational space of the starting products or the cyclisation reaction potential energy surface (PES) was explored at DFT level of theory, the polarised continuum formalism (PCM) for chloroform being used in order to consider the solvent effect. The observed stereoselection was ascribed to both the near attack conformations (NACs) distribution and the energy differences between the two possible and competitive cyclisation pathways leading to cis- and trans-diastereomers.

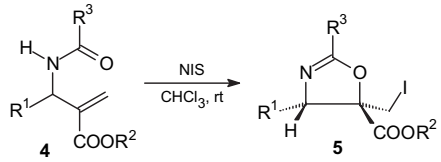
1. Introduction

3-Amino-2-hydroxy acids are compounds of particular interest owing to their biological activity. For example, *N*-benzoyl-*syn*-phenylisoserine **1a**[1] and *N*-*tert*-butoxycarbonyl-*syn*-phenylisoserine **1b**[2] occur as the C-13 side chain of paclitaxel (Taxol®)[3] and docetaxel (Taxotere®),[4] respectively. Within a research project directed to induce conformational changes in bioactive oligopeptides by means of conformationally restricted β-amino acids, starting from the Baylis–Hillman adduct **3** the racemic compounds **2a–d** were prepared, analogues of *N*-benzoyl-*syn*-phenylisoserine **1a** (Scheme 1).[5]



Scheme 1.

In the key step of the synthetic route, 3-acylamino-2-methylene-3-arylpropanoates **4** underwent iodocyclisation with NIS in chloroform[6] to give the corresponding dihydro-1,3-oxazoles **5** in high yield and with total diastereoselection (Scheme 2).[5] Thus, a computational study was initiated in order to rationalise the outcome of the cyclisation reaction.[7]



a. R^1 = Ph, R^2 = Et, R^3 = Ph
b. R^1 = Ph, R^2 = Et, R^3 = *t*-Bu
c. R^1 = 4-$CH_3OC_6H_4$, R^2 = Et, R^3 = Ph
d. R^1 = Ph, R^2 = *t*-Bu, R^3 = Ph
e. R^1 = Ph, R^2 = *t*-Bu, R^3 = Bn
f. R^1 = Ph, R^2 = *t*-Bu, R^3 = CH_2Cl
g. R^1 = Ph, R^2 = *t*-Bu, R^3 = CCl_3
h. R^1 = Me, R^2 = *t*-Bu, R^3 = CCl_3
i. R^1 = 4-NO_2-C_6H_5, R^2 = Me, R^3 = P
j. R^1 = 4-Cl-C_6H_5, R^2 = Et, R^3 = Ph
k. R^1 = Ph, R^2 = Me, R^3 = Ph

Scheme 2.

2. Computational methods

All calculations were carried out on SGI Octane2 IRIX 6.5 workstations. Molecular mechanics calculation were performed using the implementation of AMBER force field (AMBER*)[8] within the framework of Macromodel version 5.5.[9] The torsional space of each molecule was randomly varied with the usage-directed Monte Carlo conformational search.[10] For each search, at least 1000 starting structures for each variable torsion angle was generated and minimised until the gradient was less than 0.01 kcal/Åmol. Duplicate

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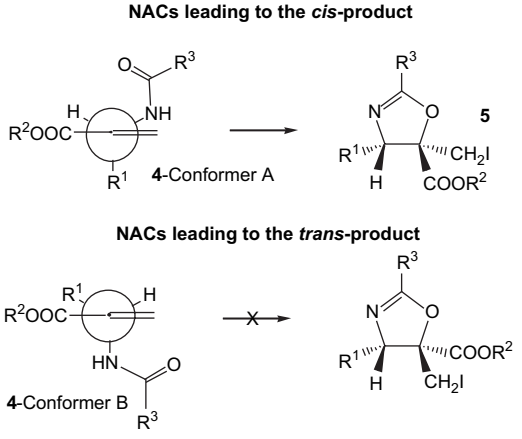
conformations and those having energy in excess of 6 kcal/mol above the global minimum were discarded. The solvent effect was included by using the implicit chloroform GB/SA solvation method of Still et al.[11]

All DFT calculations were carried out using the standard tools available in the *Gaussian 98* package,[12] with Becke's three parameter hybrid functional having the Lee–Yang–Parr correlation term (B3LYP),[13] with 6-311G** basis set for iodine and 6-31G* for all the other atoms. These functional and basis sets have been shown to properly describe the considered systems and polarisation functions are required in such calculation to obtain correct results. The transition states were searched by using the synchronous transit-guided quasi-Newton method. Frequency analyses were performed in order to obtain both energetic information about the reaction pathways and to fully characterise the nature of the stationary points onto the reaction potential energy surface (PES). The only imaginary frequency of the TS structures really corresponds to the correct reaction coordinate. Solvent effects were modelled using the polarised continuum (overlapping spheres) formalism (PCM).[14] The PCM method models the solvent as a continuum of uniform dielectric constant, and the solute is placed into a cavity within the solvent. The cavity is constructed by placing a sphere around each solute heavy atom. Hydrogen atoms are always enclosed within the sphere of the atom to which they are bonded. For the atomic radii, the Bondi approximation was used. In this method the effects of solvation are folded into the interactive SCF procedure. The dielectric constant of the solvent used was ε=4.9 (for chloroform).

3. Results and discussion

At first, in order to definitively ascertain the mechanism of the iodocyclisation reaction taking into account the experimental evidence, we fully explorated the conformational space of the starting 3-acylamino derivatives **4a–k**. This step was carried out with the aim to localise the near attack conformations (NACs)[15,16] leading to the *cis*- and *trans*-dihydro-1,3-oxazoles through the NIS mediated iodocyclisation reaction (Scheme 3).



Scheme 3. Geometry of NACs conformers of compound **4** leading to *cis*- and *trans*-dihydro-1,3-oxazoles.

Table 1. MC-search results for conformers **A** and **B** of compounds **4a–k**, obtained with 1000 step/torsional, GB/SA, $CHCl_3$, AMBER* and ΔE=6.0 kcal/mol

Compound **4**	Conformers ΔE=6.0 kcal/mol	Lowest energy conformer type A (kcal/mol)	Lowest energy conformer type B (kcal/mol)
a	52	0.0	2.60
b	44	0.0	2.69
c	132	0.0	2.38
d	23	0.0	2.25
e	41	0.0	2.27
f	18	0.0	2.23
g	13	0.0	2.08
h	11	0.0	2.97
i	28	0.0	1.71
j	35	0.0	1.60
k	24	0.0	2.62

Once the NAC has been defined, the problem can be viewed as consisting of two parts: (a) identifying ground state conformational equilibria, including formation of NACs, and (b) locating the transition state of the NAC to product. Using the energy of the conformations in a weighed Boltzmann distribution, we calculated the percentage fraction of conformers present as NACs for each compound (Table 2). Since there is a direct linear free-energy relationship between the log of the fraction of this kind of conformations and $\Delta G^{\ddagger}$, the rate constants for the cyclisation can be related to the mole fraction of the ground state of each amide present as NACs.

From the data collected, we found out two main groups of conformations, namely conformer A and B, whose structure is shown in Scheme 3. In conformer A, the iodocyclisation reaction can take place with attack of the amidic oxygen to the *re*-face of the allylic carbon, leading to the *cis*-dihydro-1,3-oxazole, while in conformer B the attack takes place on the *si*-face forming the trans-product. Since the reaction proceeds with total diastereoselection to give the cis-diastereomer, exclusively, we expect that a larger number of the NACs like A must be present and at lower energy with respect to conformations like B. Indeed, from the energetic point of view, the calculations strongly agree with the expectations (Tables 1 and 2).

Then, the geometry of each structure obtained from the conformational analysis was analysed and all the stable

Table 2. Populations of all conformers lying within 3.6 kcal/mol for compounds **4a–k**

Compounds	Population NACs cis %	Population NACs trans %	Population not-NACs
a	97.59	0.92	1.49
b	94.55	2.13	3.32
c	93.6	1.40	4.99
d	93.83	4.35	1.84
e	86.19	3.15	10.66
f	92.85	4.33	2.82
g	86.01	2.07	11.92
h	99.89	0.11	0.0
i	76.51	18.70	4.79
j	87.29	5.49	7.22
k	92.85	0.88	6.27

conformations, which lie in energy gap of 3.6 kcal/mol were classified into three categories: NACs for cis-cyclisation, NACs for trans-cyclisation and non-NACs. In Table 2, the global population of each group is summarised at T=298 K.

It was found that for all the compounds examined, the conformation type A (NACs for the observed *re*-face attack) are more populated than the corresponding type B (NACs for the not observed *si*-face attack). Since higher the population of NACs the lower is the activation energy of reaction, $\Delta G^{\ddagger}$,[16] we could immediately argue that the iodocyclisation leading to a cis-isomer is strongly favoured with respect to the iodocyclisation leading to a trans-isomer, since the molar fraction of the corresponding NACs is much larger for cis than for trans.

However, even if these data support our findings, this result alone does not completely explain the total stereoselection of the reaction, in particular for compound **4i** whose conformer type B at lower energy is significantly populated (Fig. 1).

This result prompted us to further investigate the mechanism of the iodocyclisation reaction localising the reaction paths by means of DFT quantum mechanical calculations starting from a representative compound of the amides **4a–k** having a simpler structure. Particularly, we choose the model amide **6** having R^1=*i*-Pr, R^2=*t*-Bu and R^3=CH_3, i.e., substituent groups smaller than those considered in the reported reaction (Scheme 2), which keep however the similar stereoelectronic properties. This allowed us to perform higher level ab initio calculation saving CPU time.

There are three possible reaction mechanisms, which can give rise to a cyclic product: (a) the formation of the NIS-substrate complex followed by iodonium ion formation and cyclisation (type 1); (b) the formation of the NIS-substrate complex followed by cyclisation (concerted mechanism) (type 2) and (c) the formation of the iodine cation (I^+)-substrate complex, followed by the cyclisation reaction (type 3) (Schemes 4 and 5). In order to validate or to exclude each one of these possible pathways, we localised the reaction paths onto the PES minimising the energy of all the molecular species involved (Scheme 6).

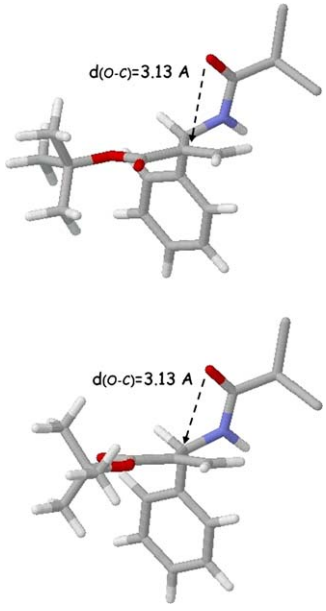
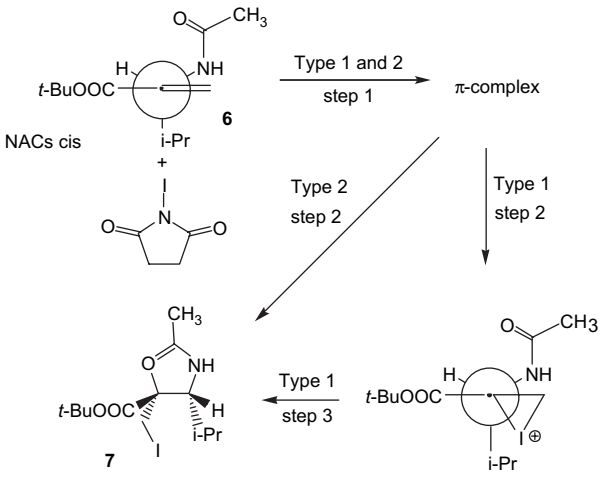


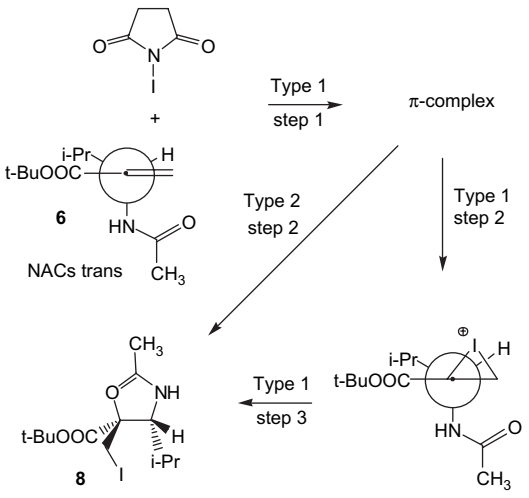
Figure 1. Lowest energy conformers (NACs for cis) for compound **4g** (type A).



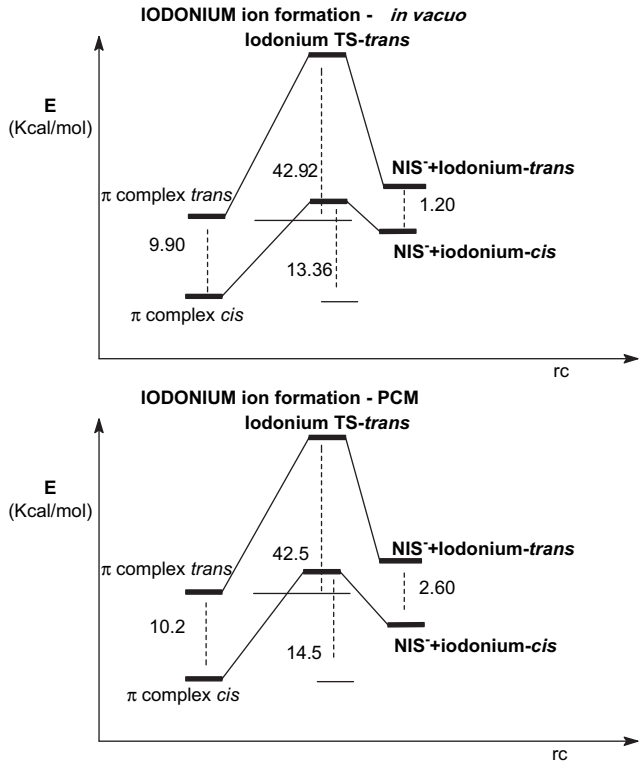
Scheme 4. Type 1 and type 2 mechanisms for iodocyclisation of **6** leading to the cis-product **7**.

Type 1 mechanism was analysed first beginning from reaction steps 1 and 2 relative to the π-complex formation for both cis- and trans-iodocyclisation. Since a complex formation is generally a very fast process, so that it cannot be involved in the stereoselectivity control, the reaction step 1 was not explicitly considered being furthermore structurally and thermodynamically very similar for both iodocyclisation reactions (namely cis and trans).

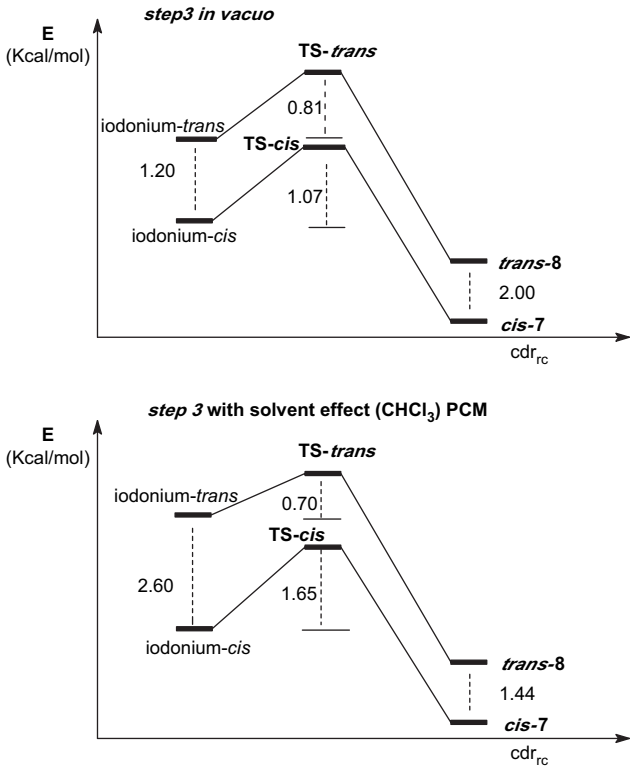
The existence of the π-complex was confirmed localising it as a stationary point onto the PES surface and also the transition state (TS) leading to the iodonium ion was found both for the cis- and trans-cyclisation (Fig. 2). All these calculations were performed in vacuo and in order to obtain more



Scheme 5. Type 1 and type 2 mechanisms for iodocyclisation of **6** leading to the trans-product **8**.



Scheme 6. Energy profiles for cis and trans-iodocyclisation step 2 (type 1 cyclisation) both in vacuo and in chloroform (PCM).



Scheme 7. Energy profiles for iodocyclisation step 3 (type 1 cyclisation) leading to either *cis*-**7** or *trans*-**8** both in vacuo and in chloroform (PCM).

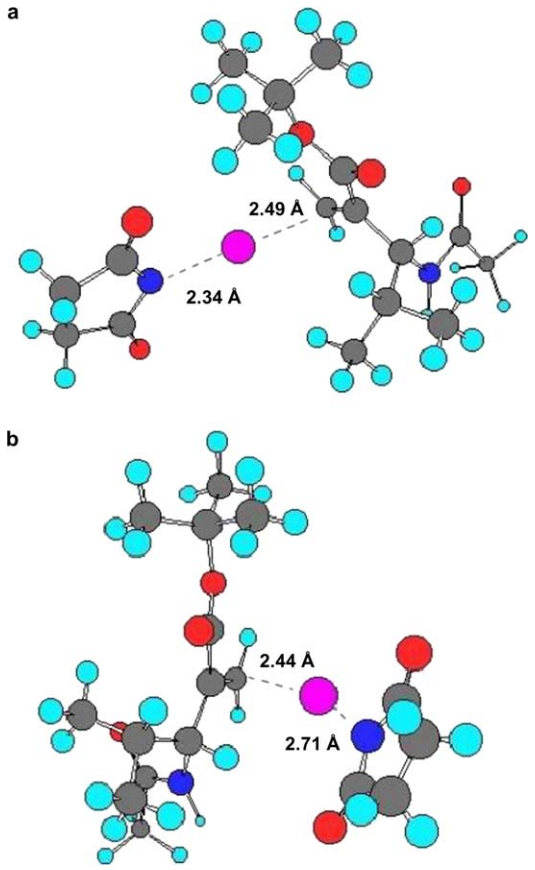


Figure 2. Transition structures of 'cis' (a) and 'trans' (b) TS of the iodonium ion formation starting from the NIS–amide–NACS π-complex (step 2).

accurate results, we included the solvent effect implicitly by using the PCM model of solvation in chloroform. When comparing the results of these two different approaches, we observed in general a change in energy but not in the relative stability of all the molecular species involved in the process.

Furthermore, for step 2 (type 1 cyclisation) it was shown that the solvent does not change the stability of the π-complex significantly or the activation energy of this step but induce a further stabilisation of the final product, *cis*-iodonium ion with respect to the trans cation.

The activation energy of this process was found to be high for the trans path and small for the *cis*-one (Scheme 7). In addition, the energy of the iodonium 'cis' is lower than the corresponding 'trans', suggesting that the cis-process is favoured over the *trans*-one by both kinetic and thermodynamic control.

When we subsequently considered step 3, the reaction pathway shows it to be fast owing to very low activation energy for both cis and trans-cyclisation processes, with the geometry of TS close to that of reagents according to the Hammond postulate (Fig. 3). Anyway, even if this step cannot affect stereoselectivity as it is too fast, the iodocylisation leading to the cis-isomer is again favoured, having a lower activation energy and forming the most stable product. From all these results, we could deduce that step 2, i.e., the formation of the π-complex, is the steady state of the overall reaction and is responsible for the stereoselection observed, according to the mechanism type 1.

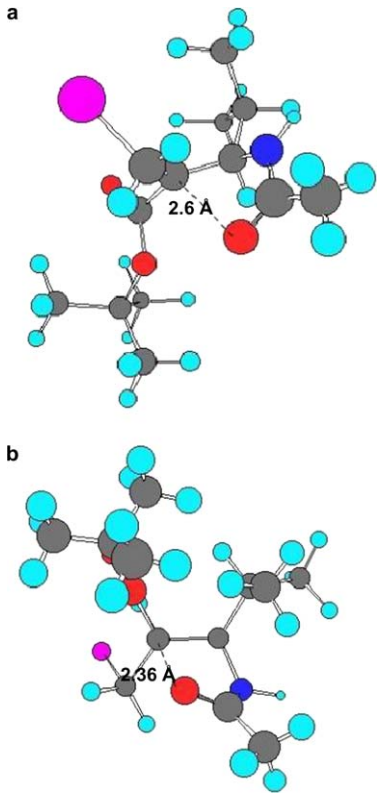


Figure 3. TS structures for type 1 mechanism step 3 leading to (a) *cis*-**7**, (b) *trans*-**8**.

These calculations were also performed both with and without considering the solvent effect, and the major changes were observed in the energy of the two iodonium cations, which have a high energy gap in relative stability (1.13 kcal/mol in vacuo, 2.57 kcal/mol in solvent) thus suggesting that stereoselection is strongly related to the formation of these two species. This result, together with the minor population of the NACs conformers leading to the trans-product, is in full agreement with the observed diastereoselection.

Eventually, although the type 1 mechanism allows explanation of the experimental data, the other mechanisms proposed must be considered, too, since they can interfere and superimpose with this latter. In particular the mechanism type 2 can compete with mechanism type 1 [i.e., iodocyclisation directly through the π-complex without formation of iodonium ion (concerted mechanism)]. However, the π-complex NIS-amide 'cis' is more stable than the NIS-amide 'trans' one, and the same is observed for the corresponding cyclic products.

Then, according to the Hammond postulate, it can be deduced that the same trend takes place for transition states observed since they are similar to the starting products. Thus, we expect that the relative activation energy has the same trend, suggesting that the observed cis-cyclisation is the more favoured process both kinetically and thermodynamically. Unfortunately the corresponding TS structures arising from these π-complexes and leading to the cyclisation product does not exist as stationary point onto the PES, automatically excluding this iodocyclisation mechanism.

At last, although intuitively it was less probable, mechanism type 3 was considered, but as expected, we were unable to find stationary points onto the PES surface corresponding to a possible π-complex between I^+ and the double bond of the substrate. In fact, all the optimisation strategies directly converge to either the iodonium ion or the cyclisation product.

4. Conclusions

From the computational results it can be strongly concluded that the stereochemical outcome of the iodocyclisation reaction of compound **3** relies on two different but concurrent aspects. On one side there is the conformational behaviour of the starting compounds, which strongly prefer to adopt a NAC arrangement leading to 'cis' iodocyclisation. On the other there is energetics of the possible reaction pathways. From the data obtained we could exclude the two competing mechanisms involving either the direct formation of the iodine cation (I^+)-substrate complex (type 3) or the π-complex (type 2) both leading to the cyclized product without involving a iodonium intermediate. Instead, we identify an exclusive reaction pathway for iodocyclisation (namely type 1), which include the formation of an iodonium cation intermediate. Furthermore from the energetics of this path, it is found that the formation of the cis-product is due to both kinetic and thermodynamic control, and thus it is the only formed product. This is in agreement with the observed stereoselectivity. Finally, even if the solvent effect is important since ionic species are involved, we must remember that the reaction is conducted in a low polarity environment (chloroform). In fact, as we can argue, we found out that this affects only the energy of the species involved and not their relative stability, thus being not able to change the nature of the mechanism itself.

Acknowledgements

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References and notes

1. For recent syntheses, see: (a) Wang, Y.; He, Q.-F.; Wang, H.-W.; Zhou, X.; Huang, Z.-Y.; Qin, Y. *J. Org. Chem.* **2006**, *71*, 1588–1591; (b) Tosaki, S.; Tsuji, R.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 2147–2155; (c) Kudyba, I.; Raczko, J.; Jurczak, J. *J. Org. Chem.* **2004**, *69*, 2844–2850; (d) Aggarwal, V. K.; Vasse, J. L. *Org. Lett.* **2003**, *5*, 3987–3990; (e) Juhl, K.; Jorgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 2420–2421.
2. (a) Torssell, S.; Kienle, M.; Somfai, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 3096–3099; (b) Borah, J. C.; Gogoi, S.; Boruwa, J.; Kalita, B.; Barua, N. C. *Tetrahedron Lett.* **2004**, *45*, 3689–3691; (c) Tadakatsu, M.; Oshitari, T.; Susowake, M. *Synlett* **2002**, 1665–1668.
3. (a) *Progress in the Chemistry of Organic Natural Products*; Herz, W., Falk, H., Kirby, G. W., Eds.; Springer: Wien, Austria, 2002; p 53; (b) Kingston, D. G. I.; Jagtap, P. G.; Yuan, H.; Samala, L. *Prog. Chem. Org. Nat. Prod.* **2002**, *84*,

53–225; (c) Gueritte, F. *Curr. Pharm. Des.* **2001**, *7*, 933–953; (d) Wang, M.; Cornett, B.; Nettles, J.; Liotta, D. C.; Snyder, J. P. *J. Org. Chem.* **2000**, *65*, 1059–1068; (e) *The Chemistry and Pharmacology of Taxol and its Derivatives*; Farina, V., Ed.; Pharmacochemistry Library; Elsevier: Amsterdam, 1995; Vol. 22.

4. Hayashi, Y.; Skwarczynski, M.; Hamada, Y.; Sohma, Y.; Kimura, T.; Kiso, Y. *J. Med. Chem.* **2003**, *46*, 3782–3784.
5. Galeazzi, R.; Martelli, G.; Mobbili, G.; Orena, M.; Rinaldi, S. *Org. Lett.* **2004**, *6*, 2571–2574.
6. (a) Orena, M. *Amination Reactions Promoted by Electrophiles*; Helmchen, G., Hofmann, R. W., Mulzer, J., Schauman, E., Eds.; Houben–Weyl, Methods of Organic Chemistry, Stereoselective Synthesis; Thieme: Stuttgart, 1995; Vol. E 2le, pp 5291–5355 and references therein; (b) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321–3408; (c) Cardillo, G.; Orena, M.; Sandri, S. *Pure Appl. Chem.* **1988**, *60*, 1679–1688.
7. (a) Chamberlin, A. R.; Mulholland, R. L., Jr.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672–677; (b) Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650–663; (c) Kahn, S. D.; Pau, C. F.; Hehre, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 7391–7399.
8. Weiner, S. J.; Kollman, P. A.; Nguyen, D. T.; Case, D. A. *J. Comput. Chem.* **1986**, *7*, 230–252.
9. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caulfield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440–467.
10. Chang, G.; Guida, W. C.; Still, W. C. *J. Am. Chem. Soc.* **1989**, *111*, 4379–4386.
11. Still, W. C.; Tempczyk, A.; Hawley, R. C.; Hendrickson, T. *J. Am. Chem. Soc.* **1990**, *112*, 6127–6129.
12. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millan, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Patersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malik, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzales, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. *Gaussian 98, Revision A.9*; Gaussian: Pittsburgh, PA, 1998.
13. (a) Becke, A. D. *J. Chem. Phys.* **1996**, *104*, 1040–1046; (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652; (c) Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200–206; (d) Becke, A. D. *Phys. Rev. A* **1988**, *58*, 3098–3100; (e) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.
14. (a) Mierts, S.; Tomasi, J. *Chem. Phys.* **1982**, *65*, 239–245; (b) Mierts, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117–129; (c) Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.* **1996**, *255*, 327–335; (d) Cancès, M. T.; Mennucci, V.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032–3041; (e) Barone, V.; Cossi, M.; Tomasi, J. *J. Comput. Chem.* **1998**, *19*, 404–417.
15. With the term near attack conformation (NAC) we define the required conformation for juxtaposed reactants to enter a transition state (TS). The greater is the mole fraction of reactant conformations that are present as NACs, the greater is the rate constant.
16. Lightstone, F. C.; Bruice, T. C. *J. Am. Chem. Soc.* **1996**, *118*, 2595–2605.