

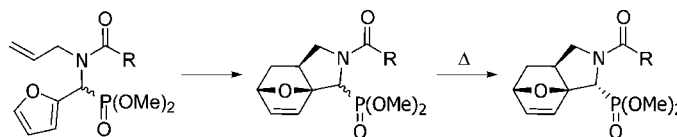
Synthesis of Tricyclic Phosphonopyrrolidines via IMDAF: Experimental and Theoretical Investigation of the Observed Stereoselectivity

Diederica D. Claeys,^{†,§,||} Kristof Moonen,[†] Bart I. Roman,^{†,||} Victor N. Nemykin,[‡]
Viktor V. Zhdankin,[‡] Michel Waroquier,[§] Veronique Van Speybroeck,^{*,§} and
Christian V. Stevens^{*,†}

Research Group SynBioC, Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure links 653, B-9000 Ghent, Belgium, Department of Chemistry and Biochemistry, University of Minnesota, Duluth, Minnesota 55812, and Center for Molecular Modeling, Ghent University, Proeftuinstraat 86, B-9000 Ghent, Belgium

chris.stevens@ugent.be; veronique.vanspeybroeck@ugent.be

Received May 28, 2008



During the synthesis of tricyclic phosphonopyrrolidines via intramolecular Diels–Alder reactions of 1-acylamino(furan-2-yl)methyl phosphonates, two isomers are formed in most cases. The presence of a short three-atom tether together with spectroscopic data, including difference NOE, revealed that the cycloaddition occurred *exo*, but the phosphonate substituent on the tether had an *exo* or *endo* orientation. This was confirmed via X-ray analysis. A thermodynamic preference for the product with the phosphonate function in the *endo* position was observed experimentally and was confirmed theoretically. Density functional theory methods and several high-level post Hartree–Fock procedures were used to rationalize the observed isomer ratio of the IMDAF-reactions. This was done for two different types of reagents: with the activating carbonyl group in the tether or as a substituent on the tether. For the first type of molecules there is a large steric hindrance of the bulky tether substituents that disfavors the *exo*-isomer. In the latter case, there was a very small energy difference between the transition states causing a mixture of epimers being formed.

Introduction

Since the discovery of the biological activity of aminoalkyl-phosphonates, e.g., as enzyme inhibitors with antibacterial, plant growth regulatory, and neuromodulatory activities,¹ many researchers have also focused their attention on conformationally constrained azaheterocyclic phosphonates.² This paper reveals the synthesis of tricyclic 2-phosphonopyrrolidines via intramo-

lecular Diels–Alder reaction of carefully designed furanyl- α -aminophosphonates. Furans can undergo Diels–Alder reactions as the 4 π diene components despite their aromaticity and hence expected decrease in reactivity,³ both inter- and intramolecularly.⁴ Furthermore, the IMDAF reaction (intramolecular Diels–Alder reaction of furan) is particularly attractive as two or more rings can be constructed in a single step with high regio- and stereocontrol, providing a convenient entry into polycyclic targets including natural products⁵ like prostaglandins^{5h,i} and terpenoids.^{5j} The 7-oxabicyclo[2.2.1]heptane skeleton, formed here, is present in biologically active natural products, but moreover, the 7-oxanorbornanes and their unsaturated deriva-

* To whom correspondence should be addressed. (C.V.S.) Fax: +32-9-2646243. Tel: +32-9-2645957. (V.V.S.) Fax: +32-9-2646697. Tel: +32-9-2646558.

[†] Department of Organic Chemistry, Ghent University.

[‡] University of Minnesota.

[§] Center for Molecular Modeling, Ghent University.

^{||} D.D.C. and B.I.R. are Ph.D. fellow of the Research Foundation - Flanders (FWO - Vlaanderen).

(1) Kafarski, P.; Lejczak, B. *Phosphorus, Sulfur, Silicon Relat. Elem.* **1991**, 63, 193–215, and references therein.

(2) (a) Moonen, K.; Laureyn, I.; Stevens, C. V. *Chem. Rev.* **2004**, 104, 6177–6215. (b) Redmore, D. *Chem. Rev.* **1971**, 71, 315–337. (c) Robiette, R.; Defacqz, N.; Peeters, D.; Marchand-Brynaert, J. *Curr. Org. Synth.* **2005**, 2, 453–477.

(3) (a) Lipshutz, B. H. *Chem. Rev.* **1986**, 86, 795–819. (b) Wenkert, E.; Moeller, P. D. R.; Piettre, S. R. *J. Am. Chem. Soc.* **1988**, 110, 7188–7194. (c) Domingo, L. R.; Picher, M. T.; Aurell, M. J. *J. Phys. Chem. A* **1999**, 103, 11425–11430. (d) Lautens, M.; Fillion, E. *J. Org. Chem.* **1996**, 61, 7994–7995.

(4) Kappe, C. O.; Murphree, S. S.; Padwa, A. *Tetrahedron* **1997**, 53, 14179–14233.

tives can undergo a variety of reactions making them quite useful synthetic intermediates in the synthesis of natural products and analogues.⁶

While absolute stereocontrol of substituents on the diene or dienophile is often observed, this is not the case for tether substituents, which regularly give mixtures of both isomers.⁷ A detailed spectroscopic elucidation of the products and their stereochemistry was performed using DIFNOE-NMR and X-ray analysis. In order to explain the origin of selectivity or duality of both isomers, theoretical calculations were conducted. They can reveal whether the process is thermodynamically or kinetically preferred and elucidate the effect of the position of the carbonyl group on the stereoselectivity. Previous studies have shown that steric interactions and ring strain in the transition states are the source of stereoselectivity in intramolecular Diels–Alder reactions.⁸ Tether substitutions, ring constraints, and (planar) functional groups are known to alter the conformational distribution and to restrict the rotations.^{9,10} The possible influence of these factors was first investigated on a compound with the carbonyl group incorporated in the tether, as a 100% selectivity was observed in that case, using DFT methods: B3LYP,¹¹ mPW1PW91,¹² and BB1K.¹³ The same DFT methods, MP2,¹⁴ MP3,¹⁵ and CCSD¹⁶ procedures were used for these compounds where both isomers were formed.

Experimental Results and Discussion

The suitability of 1-(allylamino)-1-(furan-2-yl)methyl phosphonates **5** for the IMDAF reaction was investigated. From

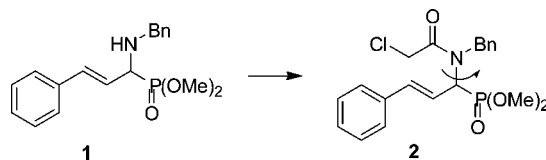


FIGURE 1. Hindered rotation after acylation of the amine.

previous research it was shown that, when aminoalkyl phosphonate **1** (Figure 1) was acylated at nitrogen, there was a hindered rotation about the C¹–N bond.¹⁷ It is, however, an unresolved issue whether this rotational barrier would allow, hinder, or proliferate the Diels–Alder reaction.

The aminoalkyl phosphonates were synthesized following our previously reported protocol.¹⁸ Subsequent acylations yielded the corresponding amides **5** in high purity (Scheme 1). With pivaloyl chloride, however, complex mixtures were obtained under different reaction conditions.

This acyl group induces both a steric and an electronic advantage to obtain a reactive substrate for the IMDAF reaction. When 1-(allylamino)-1-(furan-2-yl)methyl phosphonate **4** was refluxed overnight in toluene, only minimal amounts, 16%, of Diels–Alder adducts could be detected using the typical peaks of C⁶H₄H_b at 1.4 and 1.7 ppm. Prolonged refluxing only resulted in a breakdown of the starting material. However, when the corresponding amides (**5a–e**) were refluxed in toluene, complete conversion to the ring-closed products was observed. In all cases, a mixture of isomers (**6'** and **6''**) was formed, the identity of which will be discussed further in this paper (Scheme 1). Experiments with toluene and acetonitrile showed that the first one was the solvent of choice in most cases: a faster formation of product and smaller amounts of side products were observed, probably due to the higher boiling point of toluene.

The order of reactivity was in accordance with the results reported previously for similar substrates **7** without the phosphonate group¹⁹ (Scheme 1). With a chloroacetyl group, 20 h of reflux was required, while the ring-closed product **6e** was already formed during the acylation at room temperature and subsequent aqueous workup.

In our work, however, a remarkable influence of the phosphonate group could be observed. While amides **8a** and **8c** could only be obtained in low yield¹⁹ because of the poor conversion (Table 1), the corresponding phosphono amides **6** gave complete conversion. However, column chromatography caused big losses of the product due to the presence of a polar group such as the phosphonate group. The positive influence of increased tether substitution on IMDAF reactions is often attributed to the geminal dialkyl substitution and explained by the Thorpe–Ingold effect, the reactive rotamer, or the facilitated transition effect.^{4,20} The hindered rotation we already observed in the synthesis of phosphono-β-lactams¹⁷ will be further investigated.

The structure of the tricyclic pyrrolidines was confirmed by its 2D DQFCOSY, HSQC, and HMBC spectra (Supporting Information) and compared with the data from compounds **8**. The ¹H NMR spectrum is characterized by a large difference

(5) (a) Zhang, H. J.; Padwa, A. *Org. Lett.* **2006**, *8*, 247–250. (b) Padwa, A.; Ginn, J. D. *J. Org. Chem.* **2005**, *70*, 5197–5206. (c) Wang, Q.; Padwa, A. *Org. Lett.* **2004**, *6*, 2189–2192. (d) Kouznetsov, V. V.; Zubkov, F. I.; Cruz, U. M.; Voskressensky, L. G.; Mendez, L. Y. V.; Astudillo, L.; Stashenko, E. E. *Lett. Org. Chem.* **2004**, *1*, 37–39. (e) Fokas, D.; Patterson, J. E.; Slobodkin, G.; Baldino, C. M. *Tetrahedron Lett.* **2003**, *44*, 5137–5140. (f) Padwa, A.; Eidell, C. K.; Lynch, S. M. *Heterocycles* **2002**, *58*, 227–242. (g) Padwa, A.; Dimitroff, M.; Liu, B. *Org. Lett.* **2000**, *2*, 3233–3235. (h) Sprague, P. W.; Heikes, J. E.; Gougoutas, J. Z.; Malley, M. F.; Harris, D. N.; Greenberg, R. *J. Med. Chem.* **1985**, *28*, 1580–1590. (i) Sneden, A. T. *Synlett* **1993**, *5*, 313–322. (j) Yu, S. Y.; Beece, G.; Keay, B. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2729–2731.

(6) Vogel, P.; Cossy, J.; Plumet, J.; Arjona, O. *Tetrahedron* **1999**, *55*, 13521–13624.

(7) (a) Namboothiri, I. N. N.; Ganesh, M.; Mobin, S. M.; Cojocar, M. J. *Org. Chem.* **2005**, *70*, 2235–2243. (b) Zubkov, F. I.; Boltukhina, E. V.; Turchin, K. F.; Borisov, R. S.; Varlamov, A. V. *Tetrahedron* **2005**, *61*, 4099–4113. (c) Varlamov, A. V.; Zubkov, F. I.; Boltukhina, E. V.; Sidorenko, N. V.; Borisov, R. S. *Tetrahedron Lett.* **2003**, *44*, 3641–3643.

(8) (a) Weingarten, M. D.; Prein, M.; Price, A. T.; Snyder, J. P.; Padwa, A. *J. Org. Chem.* **1997**, *62*, 2001–2010. (b) Turner, C. I.; Williamson, R. M.; Paddon-Row, M. N.; Sherburn, M. S. *J. Org. Chem.* **2001**, *66*, 3963–3969. (c) Tantillo, D. J.; Houk, K. N.; Jung, M. E. *J. Org. Chem.* **2001**, *66*, 1938–1940.

(9) Jung, M. E.; Gervay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224–232.

(10) Bur, S. K.; Lynch, S. M.; Padwa, A. *Org. Lett.* **2002**, *4*, 473–476.

(11) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frish, M. J. *J. Phys. Chem.* **1994**, *98*, 11623–11627.

(12) Adamo, C.; Barone, V. *J. Chem. Phys.* **1998**, *108*, 664–675.

(13) (a) Zhao, Y.; Lynch, B. J.; Truhlar, D. G. *J. Phys. Chem. A* **2004**, *108*, 2715–2719. (b) BB95/6-31+G(d) IOP(3/76=0580004200).

(14) (a) Head-Gordon, M.; Pople, J. A.; Frisch, M. J. *Chem. Phys. Lett.* **1988**, *153*, 503–506. (b) Frisch, M. J.; Head-Gordon, M.; Pople, J. A. *Chem. Phys. Lett.* **1990**, *166*, 275–280. (c) Frisch, M. J.; Head-Gordon, M.; Pople, J. A. *Chem. Phys. Lett.* **1990**, *166*, 281–289. (d) Head-Gordon, M.; Head-Gordon, T. *Chem. Phys. Lett.* **1994**, *220*, 122–128. (e) Saebo, S.; Almlof, J. *Chem. Phys. Lett.* **1989**, *154*, 83–89.

(15) (a) Pople, J. A.; Seeger, R.; Krishnan, R. *Int. J. Quant. Chem. Symp.* **1977**, *11*, 149–163. (b) Pople, J. A.; Binkley, J. S.; Seeger, R. *Int. J. Quant. Chem. Symp.* **1976**, *10*, 1–19.

(16) (a) Pople, J. A.; Krishnan, R.; Schlegel, H. B.; Binkley, J. S. *Int. J. Quantum Chem.* **1978**, *14*, 545–560. (b) Bartlett, R. J.; Purvis, G. D. *J. Quant. Chem.* **1978**, *14*, 561–581. (c) Purvis, G. D.; Bartlett, R. J. *J. Chem. Phys.* **1982**, *76*, 1910–1918. (d) Scuseria, G. E.; Janssen, C. L.; Schaefer, H. F., III. *J. Chem. Phys.* **1988**, *89*, 7382–7387. (e) Scuseria, G. E.; Schaefer, H. F., III. *J. Chem. Phys.* **1989**, *90*, 3700–3703.

(17) (a) Van Speybroeck, V.; Moonen, K.; Hemelsoet, K.; Stevens, C. V.; Waroquier, M. *J. Am. Chem. Soc.* **2006**, *128*, 8468–8478. (b) Stevens, C. V.; Vekemans, W.; Moonen, K.; Rammeloo, T. *Tetrahedron Lett.* **2003**, *44*, 1619–1622. (c) Moonen, K.; Stevens, C. V. *Synthesis* **2005**, 3603–3612.

(18) Van Meenen, E.; Moonen, K.; Acke, D.; Stevens, C. V. *Arkivoc* **2006**, *i*, 31–45.

(19) Ghelfi, F.; Parsons, A. F.; Tommasini, D.; Mucci, A. *Eur. J. Org. Chem.* **2001**, 1845–1852.

(20) (a) Bruce, T. C.; Pandit, U. K. *J. Am. Chem. Soc.* **1960**, *82*, 5858–5865. (b) Parrill, A. L.; Dolata, D. P. *THEOCHEM* **1996**, *370*, 187–202.

SCHEME 1

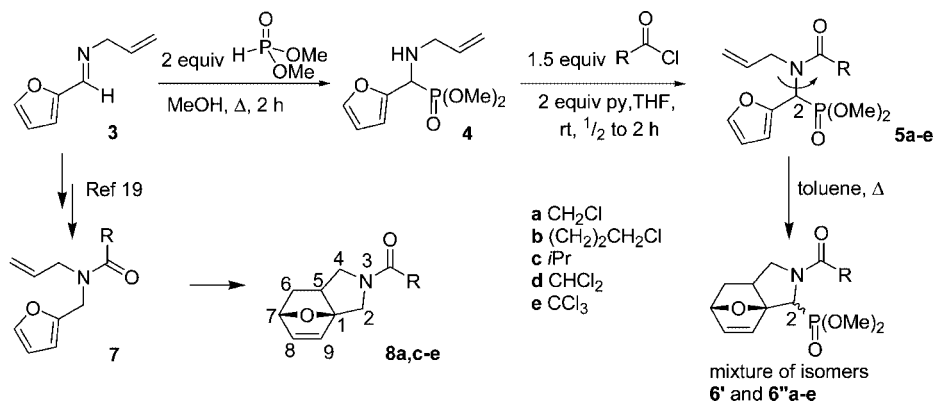


TABLE 1. Acylation and IMDAF Reaction of 1-(Allylamino)-1-(furan-2-yl)methyl Phosphonate 4

no.	R	yield of 5 (%)	conversion/yield of 6' (%)	isomer ratio 6''/6'	time (h)	<i>T</i> (°C)	conversion/yield of 7 to 8^b (%)
a	CH ₂ Cl	99	100/75	27/73	20	110	43/40
b	(CH ₂) ₂ CH ₂ Cl	88	100/47	20/80	4.5	110	
c	<i>i</i> Pr	88	100/53	17/83	7	110	62/60
d	CHCl ₂	96	100/94	35/65	3	110	100/97
e	CCl ₃	99 ^c	100/99	21/79	1 ^c	82	100/99

^a The reported yields are those of isolated products after column chromatography or crystallization. ^b 30–40 h of reflux in acetonitrile (results from ref 19). ^c The cycloadduct formed at room temperature during acylation and subsequent workup. The obtained mixture of **5e** and **6e** was further refluxed for 1 h to obtain complete conversion to **6e**.

in chemical shift of both NCH₂ protons, clearly indicating that they are on opposite sides of a rigid ring system. Similar to pyrrolidines **8**, the phosphonopyrrolidines **6** were isolated as a mixture of two isomers, indicated as **6'** and **6''** for the major and minor isomer, respectively. Ghelfi and co-workers showed, based on a NOESY experiment, that the configuration of the tricyclic skeleton in **8** was *exo* and that the two isomers were amide rotamers.¹⁹ The description *exo* is used if the group attached to a nonbridgehead atom is pointing toward the oxabridge and *endo* if it is pointing away from it. In the case of phosphonopyrrolidines **6**, the isomers might originate from three diverse structural properties: *endo*- or *exo*-annulation, amide rotamers, or configuration of the C²-center. Most studies using similar substrates show exclusive formation of the *exo*-adduct when the reaction is performed under thermodynamic control.^{4,5,7,10,19,21} *Endo*-fused, kinetic products are normally formed under high-pressure-mediated conditions.^{7a} Nevertheless, it is reasonable to suggest the appearance of an *endo*-fused isomer next to the *exo*-fused isomer based on the results of Tromp and co-workers.²² They found that more steric substituents on the tether can favor *endo*-addition. Therefore, the bulky phosphonate group may be able to alter the reaction selectivity, yielding a mixture of both adducts. However, having a close look at the ¹H NMR and DQFCOSY data of both isomers **6'** and **6''**, the differences in the multiplicities and coupling constants are found to be too little to be the result of an opposite configuration at the C⁵-bridgehead. Comparison with typical coupling constants from similar compounds revealed the presence of an *exo*-fused skeleton in both isomers (Figure 2).

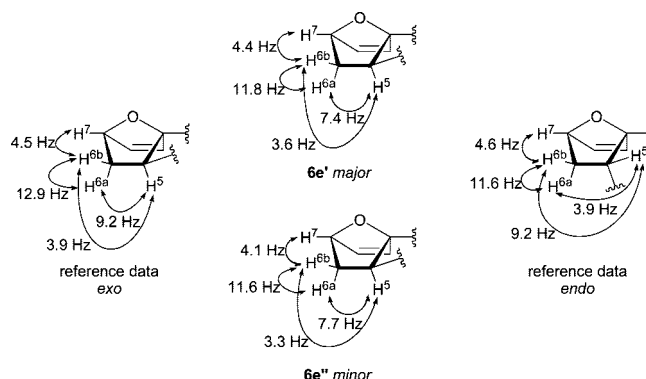


FIGURE 2. Comparison of typical coupling constants from literature sources (refs 22 and 23) with those measured in both isomers of pyrrolidine **6**.

In a further attempt to reveal the identity of the two isomers, they were separated by recrystallization in acetone or diethyl ether, giving the pure major isomer. The filtrate contained a mixture of both isomers from which the minor isomer could be recovered using column chromatography. Both isomers were stable at room temperature for at least 1 month, so no amide rotation is expected to occur during NMR acquisition. Furthermore, no rotamers were observed in the NMR spectra for the open precursors **5**. Therefore, it was concluded that the observed isomers were not rotamers but originated from an incomplete stereocontrol of the IMDAF-reaction at C².

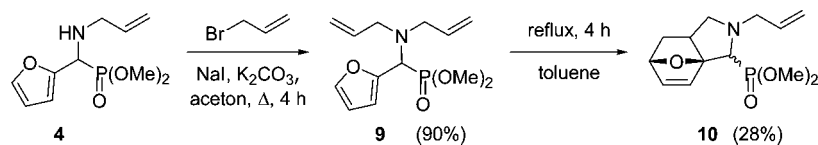
In order to reveal the position of the phosphonate group, DIFNOE experiments were performed on both isomers. Considerable nuclear Overhauser effects were observed between C⁵H and C⁶H_α and C⁴H_α, confirming the *exo*-fused skeleton of both isomers (Figure 3). A clear difference between both isomers was observed, however, when the nuclear Overhauser effect at C²H was studied: the bulky phosphonate is *exo*-oriented in the major isomer **6e'**. These results were confirmed using X-ray analysis (Figure 3).

(21) (a) Pedrosa, R.; Sayalero, S.; Vicente, M.; Casado, B. *J. Org. Chem.* **2005**, *70*, 7273–7278. (b) Padwa, A.; Ginn, J. D.; Bur, S. K.; Eidell, C. K.; Lynch, S. M. *J. Org. Chem.* **2002**, *67*, 3412–3424. (c) Paulvannan, K.; Chen, T.; Jacobs, J. W. *Synlett* **1999**, 1609–1611.

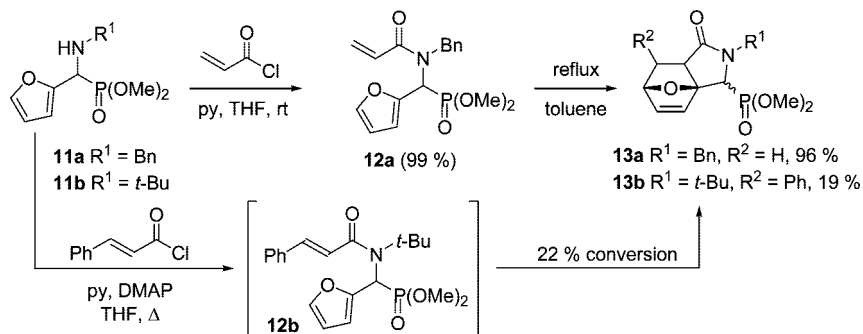
(22) Tromp, R. A.; Brussee, J.; van der Gen, A. *Org. Biomol. Chem.* **2003**, *1*, 3592–3599.

(23) (a) Feringa, B. L.; Gelling, O. J.; Melters, L. *Tetrahedron Lett.* **1990**, *31*, 7201–7204. (b) Van Royen, L. A.; Mijngheer, R.; De Clercq, P. J. *Tetrahedron Lett.* **1983**, *24*, 3145–3148.

SCHEME 2



SCHEME 3



Furthermore, the observed stereoisomer ratio may be the result of thermodynamic control and may not be the isomer ratio formed in the initial reaction mixture. Equilibration can occur under thermal conditions via a consecutive retro-Diels–Alder, Diels–Alder reaction. To investigate this kind of behavior, pure samples of major **6e'** and minor **6e''** were heated in toluene (110 °C). No change at all occurred to the minor isomer **6e''** over a 20 h period. The major isomer **6e'** on the other hand, was slowly converted to the minor isomer **6e''**. After 1 h at 110 °C, only 2% conversion was observed. This did not reflect at all the 21/79 ratio observed after 1 h at 110 °C starting from the open precursor **5e**. When heating was continued for 20 h, 95% conversion to **6e''** was observed. The slow conversion of the major isomer to the minor isomer suggests retrocycloaddition of the less stable cycloadduct. This is in agreement with the stereochemistry generally observed during IMDAF reactions: when a single bulky substituent is present in the tether, the most

stable cycloadduct will be formed in such a way as to minimize nonbonded interactions.^{7a}

Solvent effects may have an influence on the *endo/exo* selectivity.²⁴ Therefore, an experiment was set up to test this latter effect in the laboratory for the IMDAF reaction leading to pyrrolidine **6e**. Methanol, acetonitrile, and toluene were used as solvents at 65 °C leading to an *endo/exo* ratio of 18, 26, and 33%, respectively, after 2.25 h. So, the solvent does not cause an inversion of stereoselectivity, but it causes some change on the *endo/exo* ratio; the *endo* ratio increases with a decrease of the solvent polarity.

An additional experiment was performed using a substrate without an amide substituent. *N*-Allyl aminoalkyl phosphonate **4** was allylated using an excess of allyl bromide in the presence of NaI. After refluxing for 4 h in acetone, a mixture of diallylamine **9** and the ring-closed product **10** was obtained (Scheme 2). This mixture was then refluxed in toluene during 4 h, yielding the ring-closed product **10**. Notwithstanding the presence of the chiral *CHP*-center, only one isomer could be detected by NMR. Therefore, the relative stereochemistry at the *CHP*-center was apparently fixed during the ring-closure reaction or equilibration via retrocycloaddition was fast in this case.

This was also observed when the amide group was included in the tricyclic skeleton. In this case, the dienophiles were inserted during alkylation using cinnamoyl and acryloyl chloride. The corresponding pyrrolidinones **13** were obtained as single isomers upon refluxing the amides **12** in toluene or THF (Scheme 3). However, the stereochemistry of the two stereo-centers could not be determined via DIFNOE experiments. Refluxing of **13a** in toluene during 60 h did not result in formation of the other epimer. In this case the acylation of the sterically hindered *tert*-butylamine derivative succeeded, but only with a very low degree of conversion and was followed by ring closure in the same reaction step.

To conclude the experimental part learns that for compounds **6** with the acyl group as a substituent on the tether, two isomers were formed, which are epimers at the *C*²-center. The major isomer, with the phosphonate in *exo*-position, is the thermody-

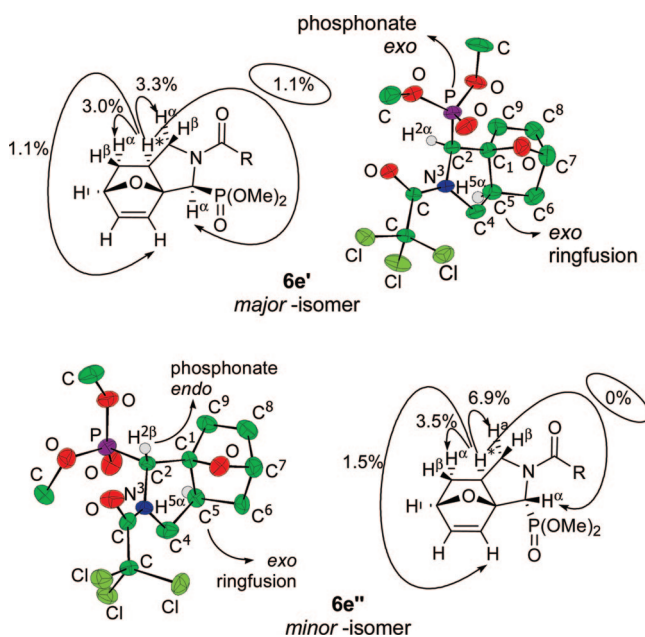
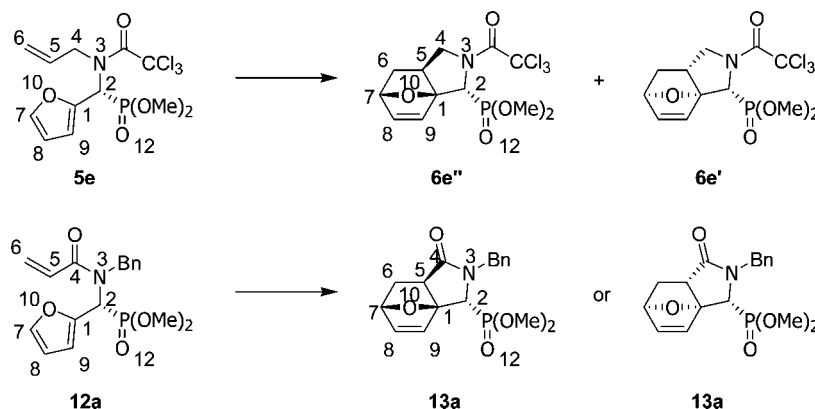


FIGURE 3. Stereochemical analysis of isomers **6e'** and **6e''**. The percentage of nuclear Overhauser effect with irradiation of *C*⁵*H* is indicated. The X-ray structures of both isomers are depicted as well.

(24) (a) Kong, S.; Evanseck, J. D. *J. Am. Chem. Soc.* **2000**, *122*, 10418–10427. (b) Moreau, Y.; Loos, P.-F.; Assfeld, X. *Theor. Chem. Acc.* **2004**, *112*, 228–239. (c) Acevedo, O.; Jorgensen, W. L. *J. Chem. Theory Comput.* **2007**, *3*, 1412–1419.

SCHEME 4. Computationally Studied IMDAF Reactions



namically less stable one. For the products **13** with the carbonyl group being part of the tether, only one isomer was formed. This isomer could not be converted into the other *C*²-epimer by refluxing it in toluene.

Computational Details

All ab initio calculations were carried out with the GAUSS-IAN 03 software package.²⁵ All geometries have been optimized at the B3LYP¹¹ level with the 6-31+G* basis set and were followed by frequency calculations that confirmed the nature of the stationary points and were used in the thermochemical analysis. Diffuse functions were added as phosphorus is a third-row element.²⁶ Previous studies have shown B3LYP is very accurate for many Diels–Alder reactions and performs well in reproducing the effects on activation energies but shows systematic errors for hetero systems and incorrectly predicts the strain of the norbornene framework, leading to an underestimation of the reaction exothermicity.^{27,28}

As a correct energy calculation of the TSs was relevant because of the small preference for one of the epimers, single-point energies were calculated with new generation functionals, i.e., mPW1PW91¹² and BB1K¹³ as well as with post-HF MP2¹⁴ and MP3¹⁵ methods, and these numbers were validated against CCSD.¹⁶

Theoretical Results and Discussion

As the tricyclic phosphonopyrrolidine **6e** was most easily formed, an X-ray was taken of both these isomers, and to have a means for comparison, **6e** was used for the calculation as well. In addition, the acryloyl derivative **13a** was used because only one isomer was formed in excellent yield. The reactions considered and the numbering of atoms are presented in Scheme 4.

Until now, we have always mentioned the formation of one or two isomers, but actually two or four different isomers are present (keeping in mind that the stereochemistry at positions

TABLE 2. Relative^a Electronic (SCF without ZPE Corrections) and Free Energies at 383.8 K (kJ/mol) for the Stationary Points of the IMDAF Reaction of **12a** to **13a** with 6-31+G(d) Basis Set

	B3LYP		BB1K		mPW1PW91	
	ΔE	ΔG	ΔE	ΔG	ΔE	ΔG
12a	0.0	0.0	0.0	0.0	0.0	0.0
TS <i>endo</i>	111.3	118.5	98.0	105.3	89.1	96.4
TS <i>exo</i>	125.6	133.8	113.8	122.0	103.8	112.0
13a <i>endo</i>	−24.6	−6.1	−72.9	−54.4	−67.3	−48.8
13a <i>exo</i>	−8.9	11.6	−57.8	−37.2	−51.5	−31.0

^a Relative to the energy of the reactant.

1, 5, and 7 are linked), since they appear as enantiomeric couples. The *R*-isomer was used for the calculations. For the product only the *exo*-oriented tether was modeled, which was based on the known stereochemical preference of the reaction. From now on, *exo* and *endo* always point at the orientation of the phosphonate group on the *C*²-position of the tether, respectively, pointing toward the oxabridge or away from it.

i. Formation of Pyrrolidinone **13a.** The relative energies and free energies of the *endo*- and *exo*-cycloadducts **13a** and their respective TSs, with respect to the reactant, are given in Table 2. The product with the phosphonate in the *endo*-position is energetically more stable than the *exo*-analogue due to reduced steric hindrance between the phosphonate group and the oxanorbornene and a higher distance between the electronegative oxygens of the phosphonate—in which the double-bonded *O* is most electronegative—and the oxabridge of the oxanorbornene skeleton. These distances are given in Table 3.

B3LYP is known to have problems with calculating the energy of the oxanorbornene skeleton.^{11,27} In this case, the relative free energies of the cycloadducts are too high and ΔG of the *exo*-isomer is even positive. Nevertheless, the energy difference between them can be used as a good indicator for their relative energetic stability, as the strain is about the same in both the *endo*- and the *exo*-isomer. This was confirmed by the good correspondence with the single-point energy calculations using the mPW1PW91¹² and BB1K¹³ functional.

The absence of a nuclear Overhauser effect between *C*⁵*H* and *C*²*H* cannot completely exclude the *exo*-position of the phosphonate, mainly because this NOE effect was small for the *exo*-isomer of pyrrolidine **6e**. An experimental indication that the *endo*-isomer is formed indeed can be deduced from the coupling constant *J*_{HP} of the proton at *C*² of product **6e**: for the *exo*-isomer this is 14.0 Hz, for the *endo*-isomer 4.7 Hz. Thus, the value of 5.5 Hz found for pyrrolidinone **13a** also points in the direction of the *endo*-isomer.

(25) Frish, M. J. et al. Gaussian 03, Revision C.02; Gaussian, Inc.: Wallingford, CT, 2004; see the Supporting Information for the full reference.

(26) (a) Leyssens, T.; Peeters, D. *THEOCHEM* **2004**, *673*, 79–86. (b) Leyssens, T.; Peeters, D. *THEOCHEM* **2004**, *686*, 71–82.

(27) Guner, V.; Khuong, K. S.; Leach, A. G.; Lee, P. S.; Bartberger, M. D.; Houk, K. N. *J. Phys. Chem. A* **2003**, *107*, 11445–11459.

(28) (a) Domingo, L. R.; Aurell, M. J.; Arno, M.; Saez, J. A. *J. Org. Chem.* **2007**, *72*, 4220–4227. (b) Pieniazek, S. N.; Houk, K. N. *Angew. Chem.* **2006**, *118*, 1470–1473. (c) Pieniazek, S. N.; Houk, K. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1442–1445. (d) Padwa, A.; Crawford, K. R.; Straub, C. S.; Pieniazek, S. N.; Houk, K. N. *J. Org. Chem.* **2006**, *71*, 5432–5439. (e) Dinadayalane, T. C.; Vijaya, R.; Smitha, A.; Sastry, G. N. *J. Phys. Chem. A* **2002**, *106*, 1627–1633. (f) Domingo, L. R.; Picher, M. T.; Andrés, J. *J. Org. Chem.* **2000**, *65*, 3473–3477.

TABLE 3. Geometric Parameters for the Stationary Points of the IMDAF Reaction of **12a** to **13a** of the B3LYP/6-31+G(d)-Optimized Structures (Distances in Å, Angles in deg)

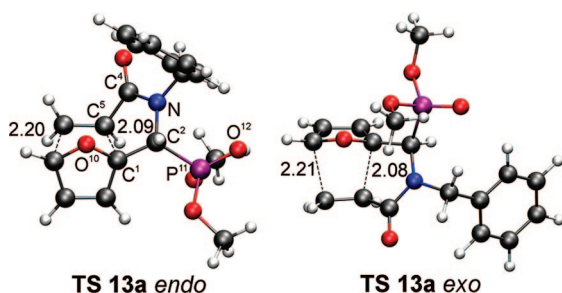
	$a_{\text{O}^{10}\text{P}^{11}}$	$a_{\text{O}^{10}\text{O}^{12}}$	$a_{\text{O}^{10}\text{O}_{\text{Cl}}^a}$	$a_{\text{H}_{\text{Bn}}\text{O}^{12}b}$	$a_{\text{H}_{\text{ar}}\text{O}^{12}c}$	$\varphi\text{C}^1\text{C}^2\text{NC}^4$	$\varphi\text{C}^2\text{NC}^4\text{C}^5$	$\varphi\text{O}^{10}\text{C}^1\text{C}^2\text{N}$
12a	4.06	4.56	4.56	4.51	4.68	120.68	−168.43	−27.15
TS <i>endo</i>	4.08	5.22	4.30	2.46	3.37	−12.49	−12.99	−71.79
TS <i>exo</i>	3.21	4.61	2.93	2.37	2.51	18.04	6.05	70.33
13a <i>endo</i>	4.09	5.23	4.27	2.52	3.21	−10.81	−6.09	−84.27
13a <i>exo</i>	3.17	4.57	2.88	2.45	2.52	16.70	1.22	80.94

^a O_{Cl} is the oxygen of the methoxy groups closest to the oxabridge. ^b H_{Bn} is the H-atom at the benzylic position closest to O¹². ^c H_{ar} is the aromatic hydrogen atom closest to O¹².

TABLE 4. Relative^a Electronic (SCF without ZPE Corrections) and Free Energies at 354.8 K (kJ/mol) for the Stationary Points of the IMDAF Reaction of **5e** to **6e** with 6-31+G(d) Basis Set

	B3LYP		BB1K		mPW1PW91		MP2		MP3		CCSD	
	ΔE	ΔG	ΔE	ΔG	ΔE	ΔG	ΔE	ΔG	ΔE	ΔG	ΔE	ΔG
5e	0.0	0.0	0.0	0.0	0.0	0.0						
TS <i>endo</i>	101.5	113.7	87.7	100.0	80.6	92.8	1.4	1.9	1.0	1.5	1.0	1.6
TS <i>exo</i>	101.9	113.6	85.4	97.2	78.7	90.4	0.0	0.0	0.0	0.0	0.0	0.0
6e <i>endo</i>	−26.0	−1.8	−76.2	−52.1	−67.7	−43.6						
6e <i>exo</i>	−12.3	9.5	−63.8	−42.0	−54.6	−32.9						

^a Relative to the energy of the reactant for DFT methods and to the TS *exo* for MPx and CCSD.

**FIGURE 4.** Structures of the TSs of the *endo*- and *exo*-isomer of **13a** at B3LYP/6-31+G(d). Distances in angstroms.

Both pathways were then explored to find an explanation for the formation of a single isomer of pyrrolidinone **13a** (Table 2). This IMDAF reaction has a large energy barrier toward the TS, which is in agreement with the high temperature required for the reaction. At 110 °C, the precursor rotamers will be in equilibrium and the kinetic isomer ratio of the cycloadducts will depend only on the difference in the free energy of the TS of both isomers (Curtin–Hammett principle²⁹). The TSs are depicted in Figure 4, and relevant geometrical parameters for TSs and precursors are given in Table 3. The free energy of the TS for the *exo*-isomer is higher than for the *endo*-isomer by 15–17 kJ/mol depending on the functional; causing the exclusive formation of the *endo*-isomer.

To trace the origin of this energetic difference, we took a closer look at the TSs and reactant. The major differences between the TSs of the different isomers are the dihedral angles $\varphi\text{O}^{10}\text{C}^1\text{C}^2\text{N}$ and $\varphi\text{C}^1\text{C}^2\text{NC}^4$. The first one corresponds to the rotation of the furan group and has an opposite value for both isomers. The latter is associated with the hindered C²–N rotation we described previously.¹⁷ This rotation has a barrier of about 70 kJ/mol at the HF/3-21+g* level and shows two minima at −45° and at 115° that have about the same energy. The *exo*-TS needs a larger distortion of the dihedral angle, and this might be one of the origins for the higher energy of the TS. This increase can be attributed to steric interactions, mainly of the benzyl and furan group with the phosphonate moiety as can be

TABLE 5. Geometric Parameters for the Stationary Points of the IMDAF Reaction of **5e** to **6e** of the B3LYP/6-31+G(d)-Optimized Structures (Distances in Å, Angles in deg)

	$a_{\text{O}^{10}\text{P}^{11}}$	$a_{\text{O}^{10}\text{O}^{12}}$	$a_{\text{O}^{10}\text{O}_{\text{Cl}}^a}$	$\varphi\text{C}^1\text{C}^2\text{NC}^4$	$\varphi\text{C}^2\text{NC}^4\text{C}^5$	$\varphi\text{O}^{10}\text{C}^1\text{C}^2\text{N}$
5e	3.14	3.50	3.07	−43.52	80.24	85.95
TS <i>endo</i>	4.08	4.59	4.54	−32.26	8.59	−61.61
TS <i>exo</i>	3.06	3.42	2.96	−23.02	49.33	92.05
6e <i>endo</i>	4.09	4.57	4.58	−25.18	8.19	−75.71
6e <i>exo</i>	3.02	3.37	2.90	−15.51	35.78	98.58

^a O_{Cl} is the oxygen of the methoxy groups closest to the oxabridge.

seen from the distances given in Table 3. The rotational potential in terms of the dihedral angle $\varphi\text{C}^1\text{C}^2\text{NC}^4$ was calculated at a B3LYP/6-31+G(d) level of theory and is given as Figure S1 in the Supporting Information.

For formation of pyrrolidinone **13a** we find exclusive formation of the *endo*-isomer corresponding to the experimental results of full selectivity, irrespective of the functional used.

ii. Formation of Pyrrolidines 6e. The energies and important geometrical parameters of the stationary points in the cycloaddition to the *exo*- and *endo*-isomer of **6e** are given in Tables 4 and 5. Again, B3LYP underestimates the free energy of the reaction, but the energy difference between both epimers is independent of the functional. The *endo*-cycloadduct is energetically preferred in order to minimize the steric hindrance and electrostatic repulsion between the phosphonate group and the oxabridge of the oxanorbornene skeleton. These distances between the oxygen atoms are listed in Table 5. The energy difference between the *endo*- and *exo*-isomer of pyrrolidinone **13a** is of the same order of magnitude as for the pyrrolidine **6e**. If the retro-Diels–Alder reaction is possible, this difference in stability between the two isomers can explain the conversion of the major isomer into the minor isomer under thermodynamic control.

Next, we wanted to unravel the experimentally observed isomer ratio during the synthesis of pyrrolidine **6e**. To test whether the Curtin–Hammett²⁹ conditions are fulfilled, the reaction was followed in methanol. Methanol was chosen because of its lower boiling point which does not allow the retro-Diels–Alder reaction to occur, as observed experimentally. Moreover, the ³¹P NMR peaks of both isomers are better

(29) Seeman, J. I. *Chem. Rev.* **1983**, 2, 83–134.

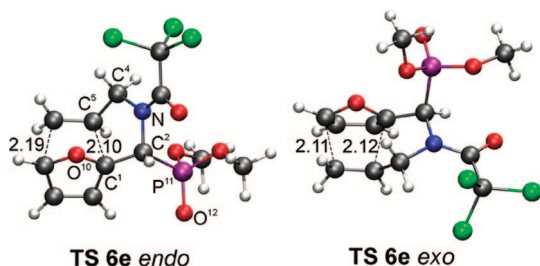


FIGURE 5. Structures of the TSs of the *endo*- and *exo*-isomer of **6e** at B3LYP/6-31+G(d). Distances in angstroms.

resolved. As the ratio of major and minor isomer remained constant throughout the course of the reaction, the Curtin–Hammett principle holds. So again the relative energies of the TSs were studied. The structures and parameters are given in Figure 5 and Tables 4 and 5. The energetic difference of both TSs is very small and depends on the functional. Therefore, a higher level of theory was used to calculate these subtle differences. MP2¹⁴ and MP3¹⁵ calculations predict indeed a lower free energy of the *exo*-TS by 1.9 to 1.5 kJ/mol, and these figures were validated using a CCSD¹⁶ calculation. This confirms the formation of a mixture of the *endo*- and *exo*-cycloadduct.

The retro-Diels–Alder reaction of the *exo*-isomer has an activation free energy that is, depending on the method, 33–42 kJ/mol more than the forward reaction and indicates that the slow thermodynamic conversion of the *exo*-isomer to the *endo*-epimer is possible.

The theoretical study for formation of pyrrolidine **6e** indeed shows that the *endo*-cycloadduct is thermodynamically preferred and that there is a competition between the formation of both isomers. CCSD calculations confirm the experimentally observed preference for the epimer in which the phosphonate group is oriented toward the oxa-bridge.

Conclusions

The IMDAF-reaction of 1-acyl-1-alkylamino(furan-2-yl)-methyl phosphonates results in complex azaheterocyclic phosphonates in a small number of synthetic steps. These products might be used as novel conformationally constrained amino acid analogues. The presence of a phosphonate substituent on the tether raises the conversion of the IMDAF reaction significantly. Furthermore, a high degree of stereocontrol is observed during the cycloaddition reaction. Only the *exo*-fused products were obtained. For derivatives containing the carbonyl group in the tether two isomers were formed, originating from incomplete stereocontrol of the phosphite addition. If the allyl group serves as dienophile, four isomers are formed resulting from an incomplete kinetic control of the position of the phosphonate as tether substituent during the IMDAF reaction. However, the most stable stereoisomers, having an *endo*-oriented phosphonate group, are formed under thermodynamic control.

This kinetic and thermodynamic control could be computationally reproduced. With the acyl group functioning as dienophile the isomers with the phosphonate group in the *exo*-position require a larger distortion from their minimum energy precursor than the *endo*-isomers and are sterically more hindered, as can be seen in their respective TSs. For aminophosphonates **5** with

the allyl group as dienophile the *endo*- and *exo*-position require about the same amide rotation and there is a subtle energy difference that requests a high level of theory calculation. From the calculations, it is clear that B3LYP fails to estimate the reaction free energy of these strained cycloadducts.

Experimental Section

Typical Procedure for the Synthesis of α -Aminophosphonates **4 and **11a,b**.** See ref 18.

Typical Procedure for the Acylation of α -Aminophosphonates (5** and **12a,b**).** To a solution of 5 mmol of 1-aminoalkyl phosphonate in 10 mL of dry THF were added 10 mmol of pyridine and a solution of the acid chloride of choice in 2 mL of dry THF under a nitrogen atmosphere. The reaction mixture was stirred for 0.5–2 h at room temperature. It was washed with saturated NaHCO_{3(aq)} and then with a 1 M HCl_(aq) solution. After drying with MgSO₄, filtration of the solids, and evaporation of the solvent under reduced pressure, the product was obtained in high purity.

Synthesis of Tricyclic Phosphonopyrrolidines. Procedure for the Preparation of Dimethyl (3-Allyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-2-yl)phosphonate (10**).** A mixture of α -amino-phosphonate **4** (5 mmol), allyl bromide (15 mmol), sodium iodide (15 mmol), and potassium carbonate (35 mmol) was refluxed in 5 mL of acetone. After 4 h, the mixture was cooled to room temperature; the insoluble salts were filtered off, and the filtrate was evaporated under reduced pressure. This resulted in a mixture of diallylamine **9** (90%) and the ring-closed product. Refluxing in toluene completed the IMDAF reaction. Product **10** was purified using column chromatography (EtOAc, *R_f* = 0.25) which caused the yield to drop to 28%.

Procedure for the Preparation of Dimethyl (3-*tert*-Butyl-4-oxo-6-phenyl-10-oxa-3-azatricyclo[5.2.1.0^{1,5}]dec-8-en-2-yl)phosphonate (13b**).** A solution of 5 mmol of 1-(*tert*-butylamino)-1-(furan-2-yl)methyl phosphonate (**11b**) and 10 mmol of pyridine in 12 mL of dry THF was stirred at room temperature under a nitrogen atmosphere. A solution of 7.5 mmol of cinnamoyl chloride in 3 mL of dry THF was added. The mixture was then refluxed for 7 h. It was washed with saturated NaHCO_{3(aq)} solution and then with 1 M HCl_(aq) and dried with MgSO₄. After filtration of the solids and evaporation of the solvent under reduced pressure, a brown oil was obtained from which the ring-closed product could be obtained in pure form using column chromatography.

Typical Procedure for the IMDAF Reaction (6** and **13a**).** A solution of 3.5 mmol of a suitable 1-(alkylamino)-1-(furan-2-yl)methyl phosphonate in 14 mL of toluene was refluxed until complete disappearance of the starting material was obtained (monitoring by ³¹P NMR). Then the solvent was removed under reduced pressure, and the corresponding adducts were obtained in good purity. Further purification could be performed using column chromatography or crystallization from ether or acetone.

Acknowledgment. We thank the Research Foundation - Flanders (Fonds voor Wetenschappelijk Onderzoek - Vlaanderen) and the research board of Ghent University for financial support of this research.

Supporting Information Available: General experimental methods, experimental procedures, spectroscopic data of all new compounds with detailed peak assignments, crystallographic information files of **6e'** and **6e''**, computational data, and full reference. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO801138S