Experimental and computational study of the ring opening of tricyclic oxanorbornenes to polyhydro isoindole phosphonates† ‡

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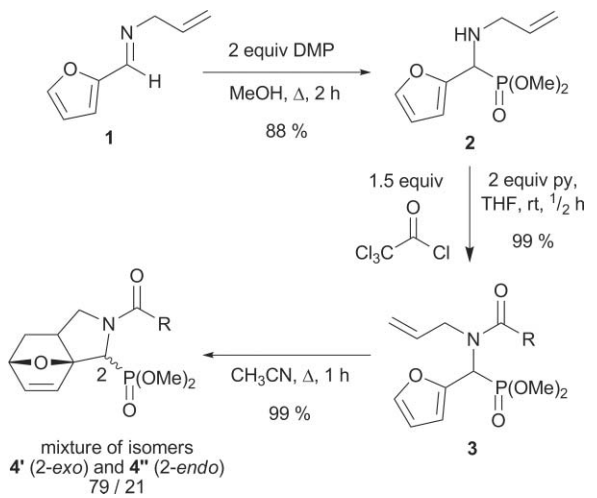
Phosphonylated azaheterocycles are an important class of compounds with high biological potential as conformationally restricted bioisosteres of amino acids. Therefore, it is of interest to synthesize conformationally constrained amino phosphonates. We wanted to investigate possible routes *via* ring opening of α-amino phosphonates with an oxanorbornene skeleton, as these can be synthesized with high stereoselectivity. This was achieved using different Lewis acids, leading to a range of products. The reaction with $TiCl_4$ and $FeCl_3$ was modelled at a DFT level of theory to get insight in the pathways towards the corresponding products. To ease the work up, the Fe(III) catalyst was coated on montmorillonite clay, but this accelerated aromatization after ring opening. Quenching the $FeCl_3$ catalyzed reaction mixture on celite caused complete aromatization.

Introduction

Phosphonic acids are known to mimic their naturally occurring carboxylic acid counterparts, notwithstanding substantial differences with respect to size, shape and acidity.[1] This is of particular importance in the field of amino acids. The use of aminophosphonates is an obvious means of constructing false substrates or inhibitors of enzymes involved in amino acid metabolism. Also neuroactive analogues of the central nervous system neurotransmitters glutamic and γ-aminobutyric acid have been prepared.[2] Besides being structural analogues of amino acids, some of the aminoalkanephosphonic acids act rather as transition state analogues, in which the tetrahedral structure of the phosphonate group resembles that of the transition state of a nucleophilic attack on an acyl group, *e.g.* of a peptide. In this way, phosphono peptides emerge as inhibitors of a wide range of enzymes. Therefore, amino phosphonates possess antibacterial, plant growth regulatory and neuromodulatory activities.[1]

Because of the success of constrained amino acids in drug design and in biomechanistic investigations,[3] also the corresponding aminophosphonic acids deserve appropriate attention. A successful example is the development of 2-aminoindane-2-phosphonic acid, which is a constrained analogue of L-phenylalanine and acts as a potent inhibitor of phenylalanine ammonia-lyase.[4] Since the discovery of the biological activity of aminoalkyl phosphonates, many researchers have also focussed their attention on azaheterocyclic phosphonates.[5] Despite the interesting potential of this class of compounds it is much less studied. Therefore, additional synthetic routes towards these conformationally constrained counterparts are of interest.

We earlier reported on the application of the intramolecular Diels–Alder reaction with furan (IMDAF reaction) in the synthesis of tricyclic phosphono pyrrolidines **4** (Scheme 1).[6] Intramolecular cycloaddition reactions such as the IMDAF reaction can achieve high levels of both regio- and stereoselectivity.[7] Only the *exo*-fused products were obtained and a combined experimental and modelling study showed that the position of the carbonyl group on the tether has an effect on the epimeric ratio of the phosphonate substituent on the pyrrolidine having an *endo*- or *exo*-position.



Scheme 1 Synthesis of tricyclic phosphono pyrrolidines **4**

Some derivatives of 7-oxabicyclo[2.2.1]heptanes (7-oxanorbornanes) are bioactive, but the 7-oxanorbornanes and their unsaturated derivatives are far more interesting for their synthetic applications.[8] Oxanorbornenes, like **4**, are known to be valuable

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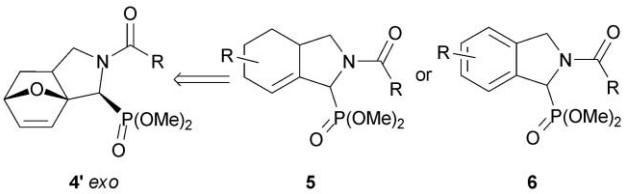
synthetic intermediates used to construct substituted arenes, carbohydrate derivatives and various natural products.[8,9] An important synthetic transformation is the breaking of the oxygen bridge.

Ring opening of the ethereal bridge of adducts **4** would result in cyclohexene derivatives like **5** which opens the possibility for the synthesis of various highly functionalized azaheterocyclic phosphonates. Aromatization during ring opening would form 1-phosphonylated 2,3-dihydro-1*H*-isoindole derivatives **6** (Scheme 2). These compounds (**5** and **6**) could be used as conformationally constrained phosphonate analogues of proline, pyroglutamic acid or phenylglycine.



Scheme 2 Possible ring-opening products of 7-oxanorbornene **4′** *exo*

Therefore, a study was initiated on the ring opening of the ethereal bridge of **4**. Different methods to achieve this have been described in literature, including treatment with acids[10,11] or bases,[12] the presence of internal electron donors,[13] nucleophilic addition[14] whether or not in combination with Lewis acids,[15] Pd(0)[16] or Rh(I)[17] catalysts, metal reduction of halides[18] and hydrogenolysis.[19] However, the presence of the phosphonate group limits the valuable possibilities.

In this article the synthesis of heterocyclic aminophosphonates starting from the IMDAF reaction is further elaborated by using different catalysts for the ring opening of the oxygen bridge, an important step in the synthesis of natural products and analogues. This is done both experimentally, by testing different catalytic systems, and computationally, by applying DFT methods to get more insight in the different ways of catalyst complexation and in the reaction pathways.

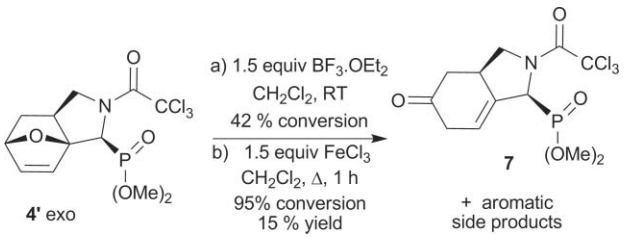
Experimental results and discussion

The reaction sequence starts with the synthesis of aminoalkyl phosphonate **2** following our previously reported protocol.[20] Then, aminophosphonate **2** was acylated, as this facilitates the IMDAF-reaction by its electronic and steric properties (Scheme 1).[21] Stirring acylaminophosphonate **3** under reflux in acetonitrile completed the IMDAF-reaction. Two epimers of tricyclic compound **4** were formed with the phosphonate in *endo* (21%) or *exo* (79%) position. The structure of the tricyclic pyrrolidines was confirmed by its 2D DQFCOSY, HSQC and HMBC spectra and on comparison with literature data[21] and is clearly outlined in previous work.[6]

The ring opening of **4′** *exo* was first evaluated with Brønsted acids, such as p-toluene sulfonic acid, glacial acetic acid or $HCl_{(aq)}$, which usually cause further aromatization; but either starting material was recovered or decomposition occurred with formation of complex reaction mixtures. Bases like NaOMe and LDA, are strong enough to deprotonate the α-position of the phosphonate resulting in the formation of a vinylic phosphonate by opening of the oxygen bridge towards a cyclohexenol derivative. Here again, no reaction occurred or the product decomposed. The ring opening with Lewis acids was more successful and is described in more detail.

$BF_3{\cdot}OEt_2$

The ring opening reaction by activation with $BF_3{\cdot}OEt_2$ had a maximal conversion of 42% to product **7** after 7 h at room temperature (Scheme 3a).



Scheme 3 Ring opening of oxanorbornene **4′** *exo* with Lewis acids to the β,γ-unsaturated phosphonate **7**

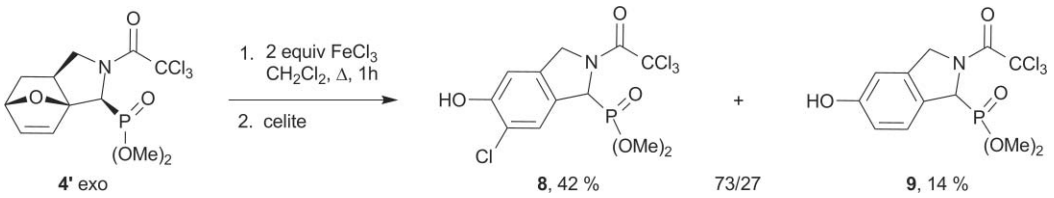
At that moment the product was not purified, but full spectral analysis, performed for the reaction with $FeCl_3$, and modelling of the reaction pathway with the $FeCl_3$ catalyst (*vide infra*) led to the conclusion that cyclohexenone derivative **7** had been formed. The C*H*P- proton is still present in the ^{1}H NMR, so no vinylic phosphonate is formed. Moreover, the ^{31}P-NMR shift of 22.6 ppm is too high to be a vinylic phosphonate, which usually appears around 16 ppm. The usually very sharp doublet of the C*H*P-proton is broadened, which is possibly caused by a very small, not resolved, allylic coupling. As only one olefinic hydrogen is present, this leads to the β,γ-unsaturated phosphonate **7** as presented in Scheme 3. A clearly unconjugated cyclic carbonyl appears at 207.5 ppm in the ^{13}C NMR and at 1718 cm^{-1} in the IR-spectrum.

$FeCl_3$

The ring opening with $FeCl_3$ gave a better conversion. However, the results can be slightly distorted as the reaction could not be followed directly by ^{31}P NMR. Fe^{3+} is paramagnetic and accelerates the longitudinal relaxation of all protons. Shorter relaxation times broaden the resonance lines and therefore $FeCl_3$ hinders the measurement of NMR spectra.[22] Therefore, the results are obtained after washing the reaction mixture several times with a saturated $NaHCO_{3(aq)}$ solution. It was assumed this did not change the ratio of the products, which implies that no phosphonic acids are formed and that the side products are mainly formed by further aromatization.

Different reaction conditions showed that catalytic amounts of Lewis acid were not sufficient. Higher reaction temperatures increased the side-product formation. The optimal conditions were one hour of reflux in dichloromethane with 1.5 equivalents of Lewis acid. About 95% conversion could be obtained, however, the reaction was not very well reproducible, probably due to the hygroscopicity of the $FeCl_3$. Unfortunately, the work-up by washing the reaction mixture several times with $NaHCO_{3(aq)}$ or $CaCO_{3(aq)}$ caused large product losses, reducing the yield to 15% only (Scheme 3b). The reaction pathway towards **7** is given in the computational part.

If the reaction mixture was filtered directly over celite and washed twice with a saturated $NaHCO_{3(aq)}$ solution to remove the Fe-residue, two products were obtained in a ratio of 73 : 27



Scheme 4 Quenching of the $FeCl_3$-catalyzed ring opening reaction of **4′** *exo* on celite causes complete aromatization to **8** and **9**

Scheme 5 Ring opening reaction of epoxide **10** to chlorohydrin **11** and cholestane-6-one **12** from literature[23] in support of the proposed mechanism for the reaction in Scheme 4

according to the integration of the ^{31}P NMR spectrum. After purification by column chromatography, they were identified as the 2,3-dihydro-1*H*-isoindole derivatives **8** and **9** (Scheme 4).

The position of the chlorine and hydroxyl group on the aromatic ring of **8** can be easily deduced from the COSY spectrum. The aromatic hydrogen in *ortho* position of the hydroxyl group will have a larger shielding or upfield shift. The most upfield aromatic proton shows a small allylic coupling with the NCH_2 protons. The most downfield aromatic proton couples with *CH*P, from which the position of the substituents can be determined. The same reasoning holds for phenol **9**, in which the aromatic proton with the most upfield broad singlet couples with the NCH_2 protons.

Apparently the work-up procedure caused a very fast aromatization of the product after possible insertion of a chloride ion. By filtration over celite, the $FeCl_3$, of which 2 equivalents were used, bound to the silicate surface, releasing chloride ions. A similar reaction was observed for a cholestane epoxide. Dry $FeCl_3$-SiO_2 reagent, formed by adsorption of $FeCl_3$ on a chromatographic silica gel, converted the epoxide **10** into a chlorohydrin (**11**) and a cholestan-6-one (**12**) (Scheme 5).[23]

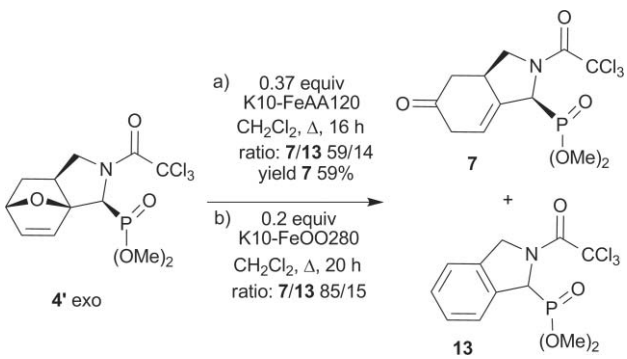
The next step was a fast oxidation, by which the $FeCl_3/SiO_2$ reacts as an oxidant.[24]

Activated montmorillonite

Because of the hygroscopicity of $FeCl_3$ and the tedious work-up, with large product losses, an alternative procedure using two different clay catalysts was evaluated.

The Fe^{3+}-cation-exchanged montmorillonite has been used as an efficient heterogeneous catalyst for the alcoholysis of epoxides,[25] which made it worth to evaluate it in the ring opening towards **7** in the absence of a nucleophile. The catalytic use of Fe^{3+}-exchanged montmorillonite clay in organic synthesis is gaining importance and has many advantages over other catalysts, such as easy handling, non corrosiveness, low cost and recovery of the catalyst.[26] Montmorillonite K10 is acid-treated, which causes delamination of the structure and creates mesopores. This augments the accessible catalytic surface, particularly at the sheet edges. A second way of activating the clay is cation exchange by metal cations such as Al^{3+} or Fe^{3+} in an aqueous medium. The Fe^{3+}-montmorillonite K10 was prepared by the procedure reported by Laszlo,[27] and activated overnight at 120 °C. This catalyst, K10-FeAA120, was evaluated for the ring opening of adduct **4′** *exo*. The clay has an estimated amount of 0.075 mmol of exchanged Fe per 0.1 g of clay.[28] This value was used for the calculation of the added equivalents of catalyst.

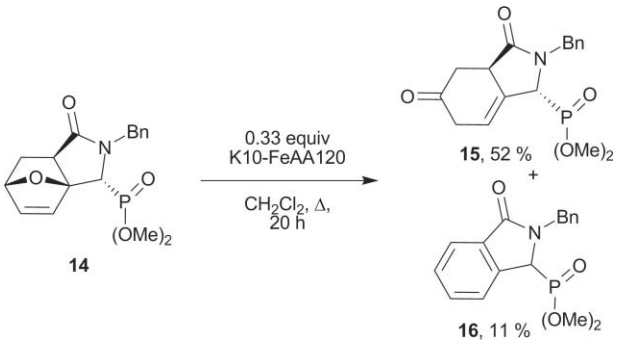
The reaction was performed in CH_2Cl_2, in which the catalyst is suspended by stirring vigorously. Optimization of the reaction conditions showed that reflux conditions are required and a catalyst load of 0.4 equivalents is necessary to reduce the reaction time and in this way, the side reactions. After 16 h, all the starting material was consumed, yielding 80% cyclohexenone **7** and 20% side-products (Scheme 6). Pure **7** could be obtained *via* column chromatography in 59% yield. The major side product (14%) was identified as the dihydroisoindole derivative **13**.



Scheme 6 Ring opening of oxanorbornene **4′** *exo* with (a) Fe^{3+}-cation-exchanged montmorillonite and (b) $FeCl_3$ adsorbed on montmorillonite K10

These optimized conditions were used for ring opening of another IMDAF adduct **14** and yielded two products in a ratio of 74 : 26. The major product was the cyclohexenone **15**, formed by the usual β-eliminative ring opening of the oxygen bridge; the minor product was the dihydroisoindolone **16** (Scheme 7).

Ferric chloride can also be adsorbed on montmorillonite K10, following a procedure by Pai *et al.*,[29] using an organic solvent. This procedure for the activation of the clay is much shorter. To leave mainly the Lewis acidity of the catalyst, it was activated at 280 °C



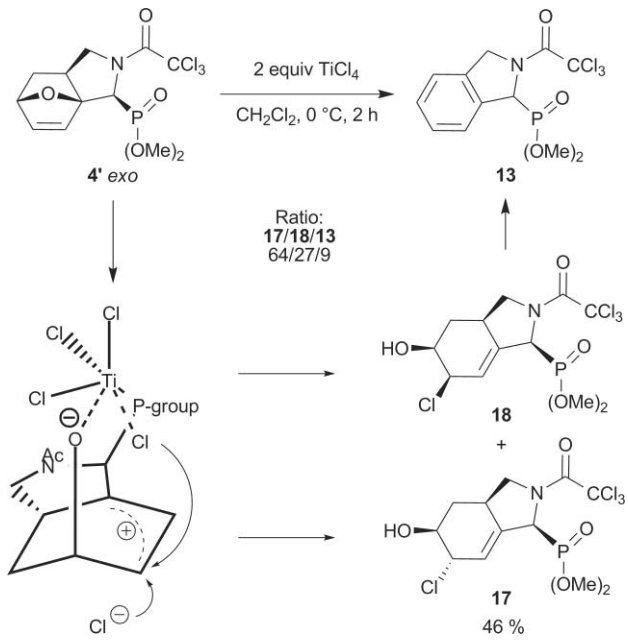
Scheme 7 Ring opening of oxanorbornene **14** with Fe^{3+}-cation-exchanged montmorillonite

before use.[30] Because of the release of minor amounts of $FeCl_3$, the interpretation and integration of the NMR spectra is hindered by peak broadening and lack of a stable deuterium lock. The catalyst, referred to as K10-FeOO280, contains about 0.063 mmol of $FeCl_3$ per 250 mg.[31]

After 20 h of reflux in CH_2Cl_2 with 0.2 equivalents of catalyst, all the starting material was consumed. Cyclohexenone **7** and dihydroisoindole **13** were formed as the only two products in a 85 : 15 ratio, according to the ^{31}P NMR values (Scheme 6). This slightly reduced aromatization can probably be ascribed to a reduced Brønsted acidity, caused by heating at 280 °C.

$TiCl_4$

$TiCl_4$ promoted the ring opening, even at 0 °C. After 2 h, the reaction was quenched by pouring the mixture in ice water. Extraction with EtOAc furnished three products: two epimers **17** and **18**, formed *via* β-eliminative bridge-opening with addition of chloride, and the dihydroisoindole derivative **13** as a minor side product (Scheme 8). Simple reflux of **17** and **18** in CH_2Cl_2 did not result in *cis–trans*-isomerisation or aromatization. The



Scheme 8 Ring opening of oxanorbornene **4′** *exo* with $TiCl_4$ catalyst via β-eliminative bridge-opening with addition of chloride

percentage of the aromatic compound **13**, was larger after chromatographic purification than before. This indicates an acid catalyzed aromatization of the cyclohexene derivative towards the dihydroisoindole. Stirring **17** and **18** on silica did indeed convert these products slowly to the aromatic compound **13**, but other unidentified (aromatic) products were formed as well. Using $Ti(OEt)_4$ would create a less acidic environment, but no reaction occurred at 0 °C, at room temperature or under reflux in CH_2Cl_2.

Given the complexation of the titanium catalyst with the oxygen bridge as depicted in Scheme 8, only the *cis* enantiomers **18** were expected, as they can be formed *via* an intramolecular reaction.[11b] In the computational part (*vide infra*) it is shown that the proposed bidentate complex is indeed the most stable way of coordination of $TiCl_4$ with **4′** *exo*. Analysis of the reaction pathway and an IRC analysis of the transition state towards **18** confirmed the concerted character of the C–O bond breaking and chloride insertion into the double bond. More details on this modelling study are given in the following section. However, after chromatographic purification of the major compound and analysing the $^2J_{HH}$ coupling constants of the cyclohexene ring, the coupling of 7.8 Hz between the protons geminal to the hydroxyl and chloro substituent, indicates this is the *trans* isomer. Comparison with literature data confirms this as shown in Fig. 1, where a *trans* coupling of 7.2 Hz was observed.[29] The formation of the *trans* isomers requires the presence of free chloride ions. These can be formed *via* complexation of $TiCl_4$ with the amide or the phosphonate or by the presence of water traces. The use of a large excess of $TiCl_4$ catalyst slightly favoured the formation of the *trans* isomer: the *cis*/*trans* ratio was 23 : 70, leaving the possibility of chloride formation by functional group complexation.

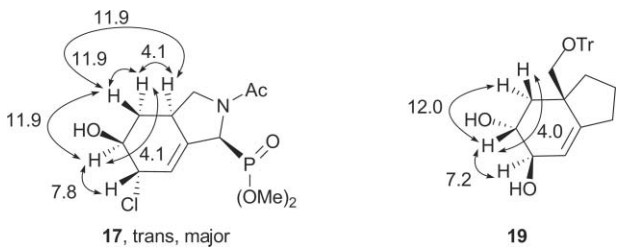
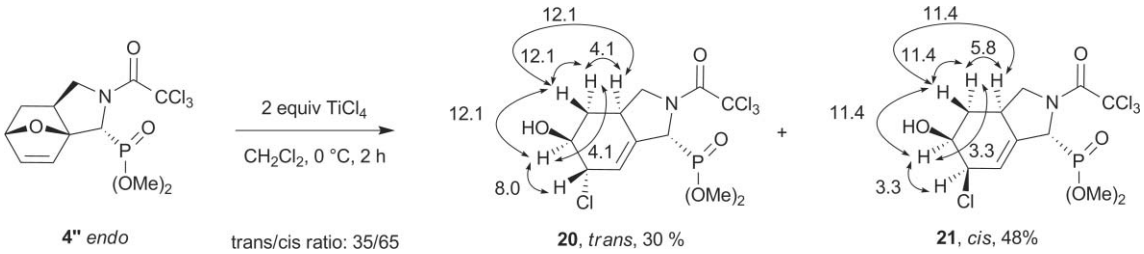


Fig. 1 $^2J_{HH}$ coupling constants of the cyclohexene ring of the major isomer **17** and comparison with compound **19** from literature.[61]

The *endo* isomer **4″**, was ring opened under the same reaction conditions. In this case no aromatic products were formed. Both products were purified by column chromatography. Again the relative stereochemistry of the hydroxyl group and the chloro substituent was determined by the $^2J_{HH}$ coupling constants of their geminal protons and these are given in Hertz in Scheme 9. A coupling constant of 8 Hz points at an almost diaxial position of the hydrogen atoms, which is only possible for the *trans* isomer. Normally the diaxial coupling is between 10 and 13 Hz, but the two vicinal equatorial substituents reduce it. For the *cis* isomer a $^2J_{HH}$ coupling of 3.3 Hz is found, slightly larger than the usual 2 Hz.

Computational details

In the literature, some assessment studies exist regarding the performance of density functionals for the description of molecular systems involving both first row transition metals and main group elements.[32–37] MP2[38] geometry optimizations have been done, but



Scheme 9 Ring opening of **4″** endo with $TiCl_4$ catalyst. The $^2J_{HH}$ coupling constants of the cyclohexene rings, used to identify both epimers **20** and **21**, are given

only for small catalytic systems.[39,40] The very popular B3LYP functional has been succesfully applied in several studies of iron and titanium systems.[41–43]

In this paper, the geometries have been optimized at the B3LYP[44] level of theory (LOT) with a LanL2DZ[45] potential for the transition metals and a 6-31g(d) basis set for the remaining atoms. This basis set is referred to as BS_1. Single point energy calculations were performed using a larger basis set: 6-311+g(3df) for Ti or Fe and 6-311+g(d) for the other atoms, which will be referred to as BS_2.

The role of dispersion interactions was evaluated using the Van der Waals correction term from B3LYP-D.[46] In this approach empirical $-C_6R^{-6}$ corrections are added to the B3LYP functional to correct for the dispersion interactions. In more general terms this approach is defined as the DFT-D methodology and has been proven very successful in many different situations.[47]

Literature data show that TPSS[48] and TPSSh[49] functionals gave promising results.[34,36] The success of TPSSh was ascribed to the 10% exact exchange by Jensen. In our paper, this functional was used for geometry optimization with a 6-311+g basis for the transition metals and a 6-31g(d) basis for the other atoms, which is referred to as BS_3. Single point energy calculations were performed using BS_2.

All geometry optimizations were followed by frequency calculations that confirmed the nature of the stationary points and that were used in the thermochemical analysis.

All *ab initio* calculations were carried out with the GAUSSIAN 03 software package,[50] except for the calculation of the B3LYP-D[47] Van der Waals corrections that were calculated with ORCA 2.6.35.[51]

In this paper, the reactions catalyzed by $FeCl_3$ and $TiCl_4$ were modelled. One of the difficulties in studying transition metal catalysts is the determination of their proper spin state. The periodic table is filled in the order [Ar] $4s^2$ $3d^{10}$, which is true for isolated metal atoms, but when a metal is surrounded with ligands, the d orbitals drop in energy and are filled first. Therefore, the electronic configuration of Fe(0), Fe with oxidation state zero, is [Ar] $4s^0$ $3d^8$; Fe(III) is [Ar] $4s^0$ $3d^5$ and Ti(IV) is [Ar] $4s^0$ $3d^0$. So, the tetrahedral $TiCl_4$ monomer has spin zero and thus multiplicity one. The $FeCl_3$ catalyst has a high-spin ground state. It prefers a half-filled d shell and has multiplicity 6. This was reported in the literature[52] and verified by us at a HF/6-31g(d) level of theory.

Computational results and discussion

The reactions with Lewis acids $TiCl_4$ and $FeCl_3$ gave different, mainly non-aromatized reaction products and the pathways given in Scheme 8 and Scheme 3b were investigated computationally.

Complexation

The complexation between oxanorbornene **4′** and both Lewis acid monomers was evaluated at different positions at B3LYP/BS_1. Both catalysts prefer coordination towards the most electronegative P=O oxygen atom over coordination towards the amide by about 35 kJ mol^{-1}. A bidentate coordination (Fig. 2) to the phosphonate and the oxygen bridge is slightly more stable (3 kJ mol^{-1} for $TiCl_4$ and 7 kJ mol^{-1} for $FeCl_3$). The substantial difference in the complexation energies of both catalysts is most probably due to the larger instability of the $FeCl_3$ monomer in the gas phase.

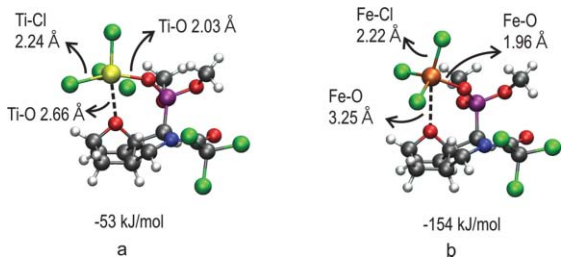


Fig. 2 Most stable, bidentate complexes between oxanorbornene **4′** and the $TiCl_4$ (a) and $FeCl_3$ (b) catalyst. The bond lengths computed at B3LYP/BS_1 are given. The complexation energy (kJ mol^{-1}) was computed at B3LYP/BS_2 // B3LYP/BS_1.

The Ti catalyst takes an octahedron-like structure in the complex with the oxanorbornene **4′** (Fig. 2a). This octahedral coordination of the $TiCl_4$ catalyst has been reported before. An *ab initio* (HF and MP3) study on the complexation of $TiCl_4$ with formaldehyde showed that formation of a six-coordinate complex *via* coordination of two carbonyl compounds is energetically preferred over a 1 : 1 complex.[53] Experimental NMR spectroscopy[54] and X-ray absorption[55] studies confirm the formation of chelate intermediates with bidentate ligands (keto esters, alkoxy ketones or alkoxy aldehydes). Octahedral 1 : 1 complexes are formed, which is in accordance with our computational results.

Iron(III) can coordinate three to eight ligands and often exhibits an octahedral coordination.[56] In this study, the Fe catalyst has a coordination number of 5 and has a trigonal bipyramidal structure. When an extra solvent molecule was added, it did not coordinate to the catalyst.

These most stable complexes were used as starting point for the evaluation of the different reaction pathways for both catalysts.

Ring opening

For the $TiCl_4$ catalyzed reaction, three pathways were investigated. (1) The minor product is formed *via* a concerted *C–O* bond

breaking and chloride transfer from the catalyst to the double bond as shown in Fig. 3, pathway **1**. An IRC calculation confirmed the concerted character of this transition state (TS **1**). (2) The energy barrier for the ring opening of the other side of the oxygen bridge was 21 kJ mol^{-1} higher than that of pathway **1** at the B3LYP/BS_1 level of theory (LOT). (3) The major product can be formed *via* addition of free chloride anions to the $TiCl_4$ complex, shown in TS **2** in pathway **2** in Fig. 3. These chloride anions result either from a strong interaction between $TiCl_4$ and the phosphonate with elimination of chloride or from the reaction of intercrystalline water with the catalyst. After opening of the oxygen bridge, the product is formed after a fast hydrolysis of the catalyst with ice water.

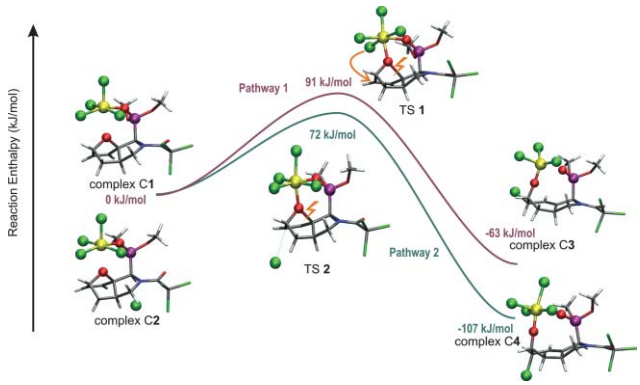


Fig. 3 Reaction profile for the ring opening of oxanorbornene **4′** with $TiCl_4$. The reaction enthalpies (ΔH) (kJ mol^{-1}) at 273.15 K were computed at the B3LYP/BS_2//B3LYP/BS_1 LOT.

The energies of the ring opening at different LOTs are given in Table 1. The energy barrier for pathway **2**, which leads to the major product is clearly lower than that of pathway **1**. Although, both pathways start from a different complex, as an external chloride anion is involved in pathway **2**, it will definitely compete

Table 1 The uncorrected electronic energies (ΔE) [a]and reaction enthalpies (ΔH) [b](kJ mol^{-1}) at 273.15 K for pathways **1** and **2** relative to the respective complexes C**1** and C**2** for the ring opening with $TiCl_4$

	Pathway **1**				Pathway **2**			
	TS **1**		Complex C**3**		TS **2**		Complex C**4**	
LOT	$\Delta E^{\ddagger}$	$\Delta H^{\ddagger}$	ΔE	ΔH	$\Delta E^{\ddagger}$	$\Delta H^{\ddagger}$	ΔE	ΔH
B3LYP/ BS_2 // B3LYP/ BS_1	98	91	−65	−63	77	72	−109	−107
B3LYP-D dispersion correction[c]	−8		2		4		6	
TPSSh/BS_2 // TPSSh/BS_3	100	93	−43	−43	72	68	−98	−95

[a] $\Delta E^{\ddagger}$: the electronic energy differences without zero-point energy corrections between the transition states (TS **1** and TS **2**) and their respective complexes (C**1** and C**2**) (Fig. 3); ΔE: the electronic energy differences without zero-point energy corrections between complex C**3** and C**1** for pathway **1** and between complex C**4** and C**2** for pathway **2** (Fig. 3). [b] $\Delta H^{\ddagger}$: the enthalpy difference with zero-point energy and thermal corrections between the transition states (TS **1** and TS **2**) and their respective complexes (C**1** and C**2**) (Fig. 3); ΔH: the enthalpy differences with zero-point energy and thermal corrections complex C**3** and C**1** for pathway **1** and between complex C**4** and C**2** for pathway **2** (Fig. 3). [c] The dispersion correction on ΔE is the difference of the dispersion correction on both single points.

Table 2 The uncorrected electronic energies (ΔE) [a]and reaction enthalpies (ΔH) [b](kJ mol^{-1}) at 313 K for pathway **3** relative to complex C**5** for the ring opening with $FeCl_3$

	TS **3**		Complex C**6**	
LOT	$\Delta E^{\ddagger}$	$\Delta H^{\ddagger}$	ΔE	ΔH
B3LYP/ BS_2 // B3LYP/BS_1	140	132	45	45
B3LYP-D dispersion correction[c]	−9		13	
TPSSh/BS_2 // TPSSh/BS_3	143	135	51	51

[a] $\Delta E^{\ddagger}$: the electronic energy differences without zero-point energy corrections between the transition state TS **3** and complex C**5** (Fig. 4); ΔE: the electronic energy differences without zero-point energy corrections between complex C**6** and complex C**5** (Fig. 4). [b] $\Delta H^{\ddagger}$: the enthalpy difference with zero-point energy and thermal corrections between the transition state TS **3** and complex C**5** (Fig. 4); ΔH: the enthalpy differences with zero-point energy and thermal corrections between the complex C**6** and complex C**5** (Fig. 4). [c] The dispersion correction on ΔE is the difference of the dispersion correction on both single points.

with the formation of minor product **17**. Comparison of the reaction enthalpies gives a similar conclusion. The electronic energy barriers computed at B3LYP and TPSSh are close to each other. The reaction enthalpies differ more. This can be due to an underestimation of the stability of the strained oxanorbornene structure at a B3LYP LOT.[6,57]

The ring opening of the oxygen bridge with ferric chloride was modelled as well. When the oxygen bridge is broken, the bond between the alkoxide and iron tightens, but no chloride ion is eliminated from the Lewis acid. Instead, the carbocation is stabilized by formation of a 3-membered epoxide (Fig. 4, pathway **3**). This epoxide (complex C**6**) is about 50 kJ mol^{-1} less stable than the starting complex C**5** of $FeCl_3$ with the oxanorbornene (Table 2). Stabilization of the transition state by one or two solvent molecules was evaluated, but these did not show explicit contacts that would stabilize the zwitterionic structure.

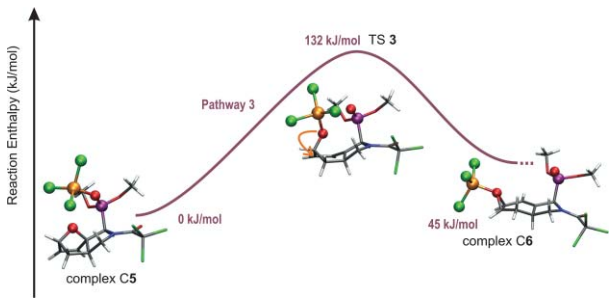
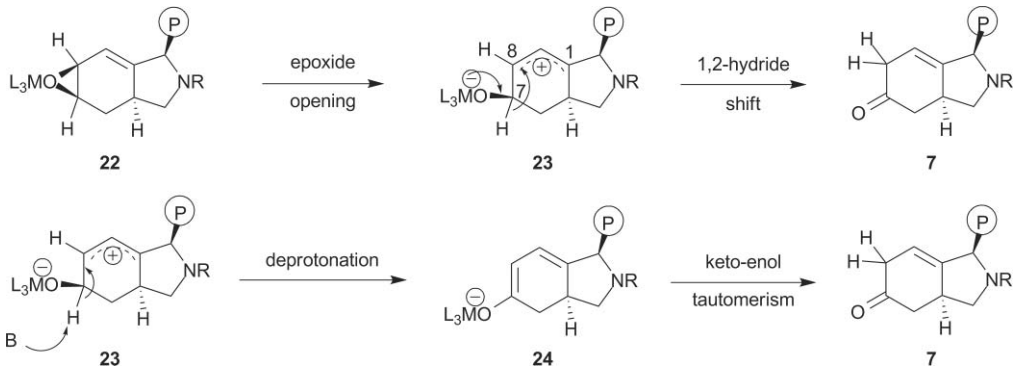


Fig. 4 Reaction profile for the ring opening of oxanorbornene **4′** with $FeCl_3$. The reaction enthalpies (ΔH) (kJ mol^{-1}) at 313 K were computed at the B3LYP/BS_2//B3LYP/BS_1 LOT.

Possible further reaction paths involve a 1-step 1,2-hydride shift of the epoxide **22** or ring opening of the epoxide and a 1,2-hydride shift from *C*(7) to *C*(8) (first pathway in Scheme 10) or deprotonation of *C*(7) followed by keto-enol tautomerism (second pathway in Scheme 10). The latter pathway was proposed by Namboothiri *et al.*[11c] Under the Lewis acidic conditions, however, it is less likely to happen.

The 1-step 1,2-hydride shift was evaluated, but a pseudo IRC analysis of the pathway at B3LYP/BS_1 predicted a large barrier of about 350 kJ mol^{-1} for this reaction.



Scheme 10 Possible further reaction paths after bridge opening with $FeCl_3$

Table 3 The uncorrected electronic energies (ΔE) [a]and reaction enthalpies (ΔH) [b](kJ mol^{-1}) at 313 K relative to complex C**5** for the 2-step 1,2-hydride shift of epoxide **22** (complex C**6**) with $FeCl_3$

	Step 1				Step2			
	TS **4**		Complex C**7**		TS **5**		Complex C**8**	
LOT	$\Delta E^{\ddagger}$	$\Delta H^{\ddagger}$	ΔE	ΔH	$\Delta E^{\ddagger}$	$\Delta H^{\ddagger}$	ΔE	ΔH
B3LYP/ BS_2 // B3LYP/BS_1	94	89	50	51	101	88	−76	−78
B3LYP-D dispersion correction[c]	10		11		11		17	
TPSSh/BS_2 // TPSSh/BS_3	108	102	59	58	116	103	−51	−52

[a] $\Delta E^{\ddagger}$: the electronic energy differences without zero-point energy corrections between the transition state and complex C**5** (Fig. 4); ΔE: the electronic energy differences without zero-point energy corrections between the intermediate complex and complex C**5** (Fig. 4). [b] $\Delta H^{\ddagger}$: the enthalpy difference with zero-point energy and thermal corrections between the transition state and complex C**5** (Fig. 4); ΔH: the enthalpy differences with zero-point energy and thermal corrections between the intermediate complex and complex C**5** (Fig. 4). [c] The dispersion correction on ΔE is the difference of the dispersion correction on both single points.

The mechanism of a 2-step acid-induced rearrangement of epoxides to ketones has been proved experimentally and computationally.[58] Also for this Lewis acid catalyzed reaction, this is a plausible pathway. The energy profile is drawn in Fig. 5 and the corresponding energies are given in Table 3.

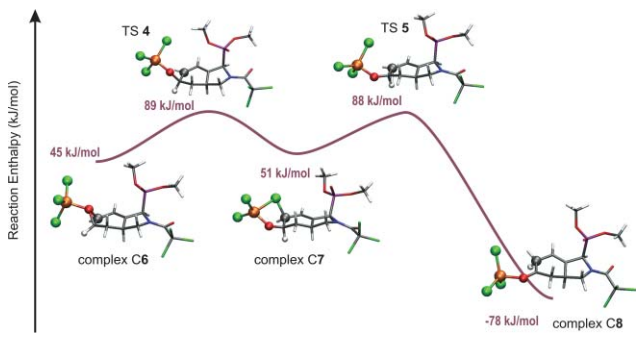


Fig. 5 Reaction profile for the 2-step 1,2-hydride shift of epoxide **22** (complex C**6**) with $FeCl_3$. The reaction enthalpies (ΔH) (kJ mol^{-1}) at 313 K were computed at the B3LYP/BS2//B3LYP/BS_1 LOT.

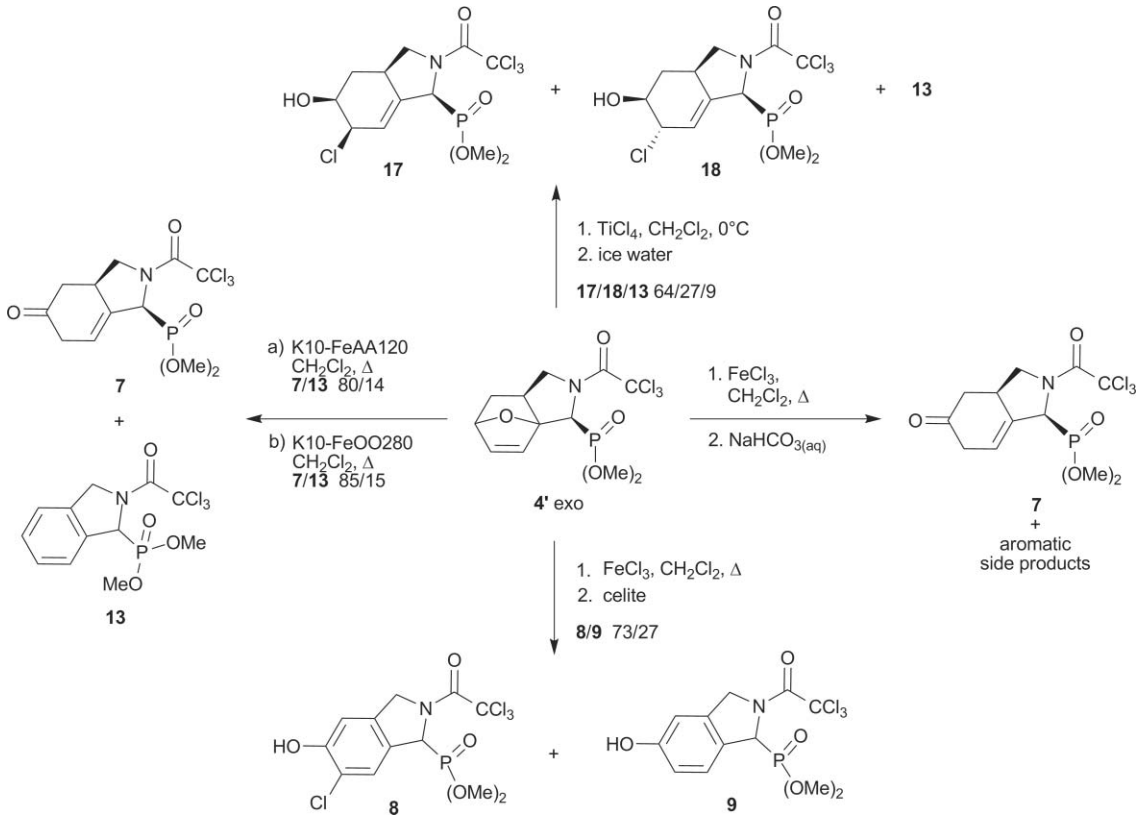
The first step is the ring opening of the epoxide **22** (complex C**6** in Fig. 5) with formation of complex C**7** in which the carbocation is stabilized by one of the chloride ligands of the Lewis acid. This step has an electronic energy barrier of 46 to 57 kJ mol^{-1} depending on the functional, B3LYP with dispersion correction or TPSSh respectively. So, whether the epoxide is formed as an intermediate or not, the pathway *via* a hydride shift remains possible, as the first step is the rate determinating step.

The next step is the 1,2-hydride shift with formation of complex C**8**, which corresponds with the experimentally observed product, ketone **7** with an energy barrier of 51 to 57 kJ mol^{-1}. For the different functionals and basis sets, this barrier is much lower than the barrier for the ring opening of the oxanorbornene.

When the two catalysts are compared, one can see that the energy barrier for breaking the *C–O* bond with $FeCl_3$ (Fig. 4) is larger than with $TiCl_4$ (Fig. 3). This corresponds with the experimental observation that the titanium catalyzed reaction completes at 0 °C and the reaction with the iron catalyst requires reflux conditions in CH_2Cl_2. The distances between *O* and *C* show that the iron catalyzed reaction has a later transition state, which is in accordance with the Hammond postulate.[59]

The main difference between the $TiCl_4$ and $FeCl_3$ as Lewis acids in the opening of the oxanorbornene oxygen bridge is their way of stabilizing the oxide anion. When the *C–O* bond is broken, the bond between the alkoxide anion and the transition metal tightens. In pathway **1** with $TiCl_4$, the alkoxide replaces a chloride that adds to the allyl cation in a concerted way. With $FeCl_3$, however, the carbocation is stabilized by the alkoxide anion itself and no chloride transfer occurs; instead, the bond with the phosphonate is broken. This behaviour coincides with the stability correlation of complexes based on Pearson's HSAB (hard-soft acid-base) principle.[60] The oxide anion is a harder ligand than the chloride and Ti(IV) is expected to be harder than Fe(III).

In the latter part, a computational basis is given for the pathways towards the main ring-opening products of the $TiCl_4$ and $FeCl_3$ catalyzed reactions. The concerted character of the ring opening with $TiCl_4$ was confirmed and indicates that the *trans* product is formed due to the presence of free chloride ions. Methods to avoid the formation of these ions should be looked for or external nucleophiles could be used to enhance *trans* isomer formation. For the ring opening with $FeCl_3$ a new pathway was proposed in which the opening of the ethereal bridge is the rate determinating step, however, aromatization remains a competitive side reaction. To avoid this, less oxidizing catalysts should be considered.



Scheme 11 Overview of the reaction conditions used for the ring opening of oxanorbornene **4′** *exo*

Conclusion

A variety of conformationally restricted α-amino phosphonates have been synthesized *via* ring opening of the ethereal bridge of IMDAF adducts **4′** *exo* and **4″** *endo*. The synthesized compounds contain the constrained phosphonate analogue of a proline, glutamic acid or phenylglycine skeleton that are important biologically active amino acids.

Different reaction conditions were found for the ring opening of the oxanorbornene **4′**, as shown in Scheme 11. The use of $FeCl_3$ and $TiCl_4$ as Lewis acids resulted in the ring opening of the oxygen bridge without complete oxidation of the six-membered ring. Aromatization causes a loss of the stereocentres that were created by the stereoselectivity of the IMDAF reaction.

Coating of the Fe-catalyst on montmorillonite K10 eased the tedious work-up, but accelerated the aromatization.

A computational study of the complexation and *C–O* bond breaking process showed that the energy barrier was higher for the $FeCl_3$-catalyzed reaction than for the $TiCl_4$-catalyzed reaction. The different behaviour of both catalysts could be linked with their affinity to form complexes with oxide anions. Using $TiCl_4$ a chloride anion was inserted to neutralize the allylic carbocation. With $FeCl_3$ the oxide anion stabilized the allylic carbocation.

Experimental section

General remarks

High-resolution ^{1}H NMR (300 MHz), ^{13}C NMR (75 MHz) and ^{31}P NMR spectra (121 MHz) were run with a Jeol Eclipse FT 300 NMR spectrometer. Peak assignments were obtained with the aid of 2D-HSQC, 2D-HMBC and 2D-COSY spectra. Low-resolution mass spectra were recorded with an Agilent 1100 Series VS>. (ES = 4000 V) mass spectrometer. IR spectra were obtained with a Perkin–Elmer Spectrum BX FT-IR System Spectrometer. Melting points of crystalline compounds were measured with a Büchi 540 apparatus and have not been corrected. The elemental analysis was performed with a Perkin–Elmer 2400 Elemental Analyzer. The purification of reaction mixtures was performed by column chromatography using a glass column with silica gel (Across, particle size 0.035–0.070 mm, pore diameter *ca.* 6 nm).

Experimental procedures

Ring opening with $FeCl_3$. To a solution of the IMDAF adduct **4′** (0.20 g, 0.5 mmol) in dry CH_2Cl_2 (10 ml), 1.5 equivalents of $FeCl_3$ (0.12 g, 0.75 mmol) were added. Care should be taken as air contact of the catalyst causes its immediate hydrolysis. After reflux under an N_2-atmosphere for 1 h, the reaction was quenched with 10 ml of a saturated $NaHCO_{3(aq)}$ solution and washed with saturated $NaHCO_{3(aq)}$ solution until the formation of yellowish $Fe(OH)_3$ complexes in the aqueous layer was no longer observed. This tedious work-up delivered the cyclohexenone **7** (0.03 g, 15%).

*Dimethyl (1*S*,3a*R*)- and (1*R*,3a*S*)-[5-oxo-2-(2,2,2-trichloroacetyl)-2,3,3a,4,5,7a-hexahydro*-1H-*isoindol-1-yl] phosphonate (7).* (Found: C, 37.0; H, 3.9; N, 3.6. $C_{12}H_{15}Cl_3NO_5P$ requires C, 36.9; H, 3.9; N, 3.6%); ν_{max}(film)/cm^{-1} 1038 (P–O), 1254 (P=O), 1677 (C=O) and 1718 (C=O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.29 (1H, dd, J = 15.1 Hz and J = 12.5 Hz, CH_AH$_B$CH), 2.73

(1H, dd, J = 15.1 Hz and J = 5.0 Hz, CH_AH_BCH), 2.86–2.99 (1H, m, CH_AH_BCH=), 3.03–3.16 (2H, m, CH_AH_BCH= and CH), 3.50 (1H, t, J = 11.2 Hz, NCH_AH_B), 3.79 (3H, d, J_{HP} = 10.7 Hz, OCH_3), 3.89 (3H, d, J_{HP} = 10.7 Hz, OCH_3), 4.75 (1H, dd, J = 11.2 Hz and J = 7.7 Hz, NCH_AH_B), 5.36 (1H, br d, J_{HP} = 13.8 Hz, CHP), 6.26 (1H, octuplet, J = 2.5 Hz, =CH); δ_C (75 MHz; $CDCl_3$; Me_4Si) 39.13 (CH_2CH=), 39.68 (CH), 42.00 (CH_2CH), 53.68 (d, J_{CP} = 6.9 Hz, OCH_3), 53.94 (d, J_{CP} = 5.8 Hz, OCH_3), 54.81 (NCH_2), 57.28 (d, J_{CP} = 156.9 Hz, CHP), 92.67 (C_qCl_3), 119.15 (d, J_{CP} = 6.9 Hz, HC=C), 134.55 (d, J_{CP} = 4.6 Hz, C_q=CH), 159.01 (C=O, amide), 207.52 (C=O, ketone); δ_P (121 MHz; $CDCl_3$) 22.60; m/z (ESI) 390/392/394 $[M+H]^+$; Chromatography: R_f 0.21 (EtOAc).

Ring opening with $FeCl_3$ followed by filtration over celite. To a solution of the IMDAF adduct **4′** (0.20 g, 0.5 mmol) in dry CH_2Cl_2 (10 ml), 2.0 equivalents of $FeCl_3$ (0.17 g, 1.0 mmol) were added. Care should be taken as air contact of the catalyst causes its immediate hydrolysis. After reflux under an N_2-atmosphere for 1 h, the suspension was filtered directly over celite. The residue was washed with CH_2Cl_2 (10 ml). The filtrate was washed 3 times with an equal amount of saturated $NaHCO_{3(aq)}$ solution. This yielded dihydroisondoles **8** and **9** in a ratio of 73 : 23. Purification by column chromatography furnished pure **8** (0.09 g, 42%) as colourless crystals and **9** (0.03 g, 14%) as a yellow oil.

Dimethyl [6-chloro-5-hydroxy-2-(2,2,2-trichloroacetyl)-2,3-dihydro-1H-*isoindol-1-yl]phosphonate (**8**).* (Found: C, 34.1; H, 2.8; N, 3.3. $C_{12}H_{12}Cl_4NO_5P$ requires C, 34.1; H, 2.9; N, 3.3%); ν_{max}(film)/cm^{-1} 1035 (P–O), 1687 (C=O), 3142 (OH); δ_H (300 MHz; $CDCl_3$; Me_4Si) 3.72 (3H, d, J = 10.5 Hz, OCH_3), 3.90 (3H, d, J = 11.0 Hz, OCH_3), 5.00 (1H, dd, J = 14.6 Hz and J = 5.2 Hz, CH_aH_bN), 5.35 (1H, dd, J = 14.6 Hz and J = 6.9 Hz, CH_aH_bN), 5.78 (1H, d, J_{HP} = 8.8 Hz, CHP), 6.71 (1H, s, $CH_{ar}COH$), 7.43 (1H, d, J = 2.2 Hz, $CH_{ar}CCl$); δ_C (75 MHz; $CDCl_3$; Me_4Si) 53.86 (d, J_{CP} = 6.9 Hz, OCH_3), 54.27 (d, J_{CP} = 6.9 Hz, OCH_3), 54.82 (CH_2N), 61.46 (d, J_{CP} = 156.9 Hz, CHP), 92.64 (C_qCl_3), 110.29 ($CH_{arom}C_{q,arom}OH$), 120.63 ($C_{q,arom}Cl$), 124.53 (d, J_{CP} = 5.8 Hz, $C_{q,arom}CH_2$), 124.64 (d, J_{CP} = 3.5 Hz, $CH_{arom}C_{q,arom}Cl$), 137.44 (d, J = 4.6 Hz, $C_{q,arom}CHP$), 152.81 ($C_{q,arom}OH$), 159.61 (C=O); δ_P (121 MHz; $CDCl_3$) 21.78; m/z (ESI) 422/424/426/428 $[M+H]^+$; mp 198 °C (carbonization, from EtOAc); chromatography R_f 0.27 (EtOAc/PE 12 : 5).

Dimethyl [5-hydroxy-2-(2,2,2-trichloroacetyl)-2,3-dihydro-1H-*isoindol-1-yl]-phosphonate (**9**).* (Found: C, 37.0; H, 3.4; N, 3.6. $C_{12}H_{13}Cl_3NO_5P$ requires C, 37.1; H, 3.4; N, 3.6%); ν_{max}(film)/cm^{-1} 1032 (P–O), 1684 (C=O), 3205 (OH); δ_H (300 MHz; $CDCl_3$; Me_4Si) 3.72 (3H, d, J = 10.5 Hz, OCH_3), 3.90 (3H, d, J = 11.0 Hz, OCH_3), 5.02 (1H, dd, J = 14.3 Hz and J = 5.0 Hz, CH_aH_bN), 5.35 (1H, dd, J = 14.3 Hz and J = 6.6 Hz, CH_aH_bN), 5.80 (1H, d, J_{HP} = 7.7 Hz, CHP), 6.55 (1H, s, $C_{q,ar}CH_{ar}COH$), 6.63 (1H, d, J = 8.3 Hz, $CH_{ar}CH_{ar}COH$), 7.21 (1H, dd, J = 8.3 Hz and J = 1.7 Hz, $C_{q,ar}CH_{ar}CH_{ar}$); δ_C (75 MHz; $CDCl_3$; Me_4Si) 53.69 (d, J_{CP} = 5.8 Hz, OCH_3), 54.25 (d, J_{CP} = 6.9 Hz, OCH_3), 55.12 (CH_2N), 61.48 (d, J_{CP} = 158.1 Hz, CHP), 92.68 (C_qCl_3), 109.58 ($C_{q,ar}CH_{ar}COH$), 115.84 ($CH_{ar}CH_{ar}COH$), 122.40 (d, J_{CP} = 4.6 Hz, $C_{q,ar}CHP$), 124.54 ($C_{q,ar}CH_{ar}CH_{ar}$), 138.61 (d, J_{CP} = 5.8 Hz, $C_{q,ar}CH_2$), 157.84 ($C_{q,ar}OH$), 159.52 (C=O); δ_P (121 MHz; $CDCl_3$) 22.41; m/z (ESI) 388/390/392 $[M+H]^+$; Chromatography R_f 0.15 (EtOAc/PE 12 : 5).

Ring opening using Fe^{3+}-montmorillonite.

General procedure for the ring opening with K10-FeAA120. To a solution of the IMDAF adduct (0.20 g, 0.5 mmol of **4′** and 0.17 g, 0.5 mmol of **14**) in dry dichloromethane, K10-FeAA120 (0.25 g) was added. This mixture was stirred vigorously and refluxed for 16–20 h depending on the substrate. After filtration of the clay catalyst, the solvent was evaporated under reduced pressure. Product **7** was purified *via* column chromatography (0.12 g, 59%), the major aromatic side-product **13** (14%) was fully identified in the reaction with $TiCl_4$. Cyclohexenone **15** (0.09 g, 52%) and dihydroisoindole **16** (0.02 g, 11%) were purified using preparative TLC.

*Dimethyl (1*S*,3a*R*)- and (1*R*,3a*S*)-(2-benzyl-3,5-dioxo-2,3,3a,4,5,7a-hexahydro*-1H-*isoindol-1-yl) phosphonate (**15**).* (Found: C, 58.5; H, 5.8; N, 4.1. $C_{17}H_{20}NO_5P$ requires C, 58.5; H, 5.8; N, 4.0%); ν_{max}(film)/cm^{-1} 1033 (P–O), 1232 (P=O), 1686 (C=O), 1702 (C=O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.33 (1H, dd, J = 15.4 Hz and J = 12.7 Hz, CH_AH_BCH), 2.93–3.00 (2H, m, CH_2CH=), 3.00 (1H, dd, J = 15.4 Hz and J = 5.8 Hz, CH_AH_BCH), 3.51–3.63 (1H, m, CH), 3.80 (3H, d, J_{HP} = 10.7 Hz, OCH_3), 3.84 (3H, d, J_{HP} = 10.2 Hz, OCH_3), 4.18–4.22 (1H, m, CHP), 4.24 (1H, d, J = 14.9 Hz, NCH_AH_B), 5.32 (1H, d, J = 14.9 Hz, NCH_AH_B), 5.87–5.94 (1H, m, =CH), 7.22–7.39 (5H, m, CH_{arom}); δ_C (75 MHz; $CDCl_3$; Me_4Si) 39.28 (CH_2CH=), 39.46 (CH_2CH), 40.93 (CH_2CH), 45.28 (NCH_2), 53.38 (d, J_{CP} = 8.0 Hz, OMe), 54.26 (d, J_{CP} = 8.0 Hz, OMe), 56.60 (d, J_{CP} = 160.4 Hz, CHP), 121.77 (d, J_{CP} = 9.2 Hz, CH=), 128.11 (CH_{arom}), 128.43 (2 × CH_{arom}), 129.02 (2 × CH_{arom}), 130.41 (d, J_{CP} = 6.9 Hz, C_q=), 135.38 ($C_{q,arom}$), 173.29 (C=O, lactam), 206.62 (C=O, ketone); δ_P (121 MHz; $CDCl_3$) 21.71; m/z (ESI) 350 $[M+H]^+$; chromatography R_f 0.16 (EtOAc/PE 7 : 3).

Dimethyl (2-Benzyl-3-oxo-2,3-dihydro-1H-*isoindol-1-yl)phosphonate (**16**).* (Found: C, 61.6; H, 5.5; N, 4.2. $C_{17}H_{18}NO_4P$ requires C, 61.6; H, 5.5; N, 4.2%); ν_{max}(film)/cm^{-1} 1029 (P–O), 1257 (P=O), 1692 (C=O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 3.56 (3H, d, J_{HP} = 10.7 Hz, OCH_3), 3.74 (3H, d, J_{HP} = 10.7 Hz, OCH_3), 4.55 (1H, d, J = 15.0 Hz, NCH_AH_B), 4.69 (1H, d, J_{HP} = 13.2 Hz, CHP), 5.58 (1H, d, J = 15.0 Hz, NCH_AH_B), 7.23–7.35 (5H, m, CH_{arom}), 7.51–7.61 (2H, m, CH_{arom}), 7.67–7.72 (1H, m, CH_{arom}), 7.91–7.96 (1H, m, CH_{arom}); δ_C (75 MHz; $CDCl_3$; Me_4Si) 45.12 (NCH_2), 53.77 (d, J_{CP} = 6.9 Hz, 2 × OCH_3), 56.92 (d, J_{CP} = 155.8 Hz, CHP), 124.19 (CH_{arom}), 124.45 (d, J_{CP} = 2.3 Hz, CH_{arom}), 127.76 ($CH_{arom,benzyl}$), 128.39 (2 × $CH_{arom,benzyl}$), 128.79 (2 × $CH_{arom,benzyl}$), 129.03 (CH_{arom}), 131.84 (CH_{arom} and $C_{q,arom}$), 136.65 ($C_{q,arom,benzyl}$), 138.44 (d, J_{CP} = 5.8 Hz, $C_{q,arom}$), 168.83 (d, J_{CP} = 3.5 Hz, C=O); δ_P (121 MHz; $CDCl_3$) 21.05; m/z (ESI) 332 $[M+H]^+$; chromatography R_f 0.29 (EtOAc/PE 7 : 3).

Ring opening with $TiCl_4$. A solution of the IMDAF adduct (0.20 g, 0.5 mmol) in dry dichloromethane (20 ml) was cooled in an ice bath. With a syringe with a small amount of purified petroleum ether in it, 2 equivalents of $TiCl_4$ (0.11 ml, 1.0 mmol) were added. (To purify the petroleum ether, it was washed with 18 M H_2SO_4 in a separatory funnel, next the organic solvent was treated with K_2CO_3.) The reaction mixture was stirred for 2 h at 0 °C under an N_2-atmosphere, poured into 20 ml of ice water and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and filtered. The solvent was removed under reduced pressure. The residue was subjected to column chromatography to yield the

cis and *trans* cyclohexenes (**17**: 0.10 g, 46%; **20**: 0.07 g, 30%; **21**: 0.11 g, 48%) and the aromatized product (**13**: 0.02 g, 11%) in case IMDAF adduct **4′** was used.

*Dimethyl (1S,3aR,5S,6S)- and (1R,3aS,5R,6R)-[6-chloro-5-hydroxy-2-(2,2,2-trichloroacetyl)-2,3,3a,4,5,6-hexahydro-*1H*-isoindol-1-yl] phosphonate (**17**).* (Found: C, 33.7; H, 3.7; N, 3.2. $C_{12}H_{16}Cl_4NO_5P$ requires C, 33.8; H, 3.8; N, 3.3%); ν_{max}(film)/cm^{-1} 1027 (P–O), 1677 (C=O), 3387 (OH); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.57 (1H, q, J = 11.9 Hz, CH_aH_b), 2.28 (1H, dt, J = 11.9 Hz and J = 4.1 Hz, CH$_a$$H_b$), 2.58 (1H, br s, O$H$), 2.80–2.97 (1H, m, C$H$), 3.30 (1H, t, J = 11.1 Hz, CH_aH_bN), 3.77 (3H, d, J = 11.0 Hz, OCH_3), 3.87 (3H, d, J = 11.0 Hz, OCH_3), 4.04 (1H, ddd, J = 11.9 Hz, J = 7.8 Hz and J = 4.1 Hz, CHOH), 4.55–4.63 (1H, m, CHCl), 4.61 (1H, dd, J = 11.1 Hz and J = 7.7 Hz, CH$_a$$H_b$N), 5.29 (1H, dq, J_{HP} = 14.6 Hz and J = 2.2 Hz, CHP), 6.18–6.23 (1H, m, HC=C); δ_C (75 MHz; $CDCl_3$; Me_4Si) 33.57 (*C*H$_2$), 40.97 (d, J_{CP} = 2.3 Hz, *C*H), 53.85 (d, J_{CP} = 8.1 Hz, OCH$_3$), 54.04 (d, J_{CP} = 5.8 Hz, OCH$_3$), 54.40 (*C*H$_2$N), 56.83 (d, J_{CP} = 158.1 Hz, *C*HP), 63.95 (d, J_{CP} = 3.5 Hz, *C*HCl), 74.00 (*C*HOH), 92.70 (C$_q$Cl$_3$), 122.38 (d, J_{CP} = 6.9 Hz, H*C*=C), 137.79 (d, J_{CP} = 4.6 Hz, HC=*C*), 159.24 (C=O); δ_P (121 MHz; $CDCl_3$) 22.14; *m*/*z* (ESI) 426/428/430/432 [M+H]$^+$; chromatography R_f 0.05 (EtOAc/PE 3 : 2).

*Dimethyl (1S,3aR,5S,6R)- and (1R,3aS,5R,6S)-[6-chloro-5-hydroxy-2-(2,2,2-trichloroacetyl)-2,3,3a,4,5,6-hexahydro-*1H*-isoindol-1-yl] phosphonate (**18**).* The spectrum was derived from the spectral data of the mixture of the cyclohexene derivatives. δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.65 (1H, q, J = 11.5 Hz, CH_aH_b), 2.07 (1H, ddd, J = 11.5 Hz, J = 4.8 Hz and J = 3.4 Hz, CH$_a$$H_b$), 2.72–2.97 (1H, m, C$H$), 3.30 (1H, t, J = 11.6 Hz, CH_aH_bN), 3.81 (3H, d, J = 11.0 Hz, OCH_3), 3.86 (3H, d, J = 10.5 Hz, OCH_3), 4.00–4.08 (1H, m, CHOH), 4.55–4.65 (1H, m, CH$_a$$H_b$N), 4.87 (1H, br s, C$H$Cl), 5.27 (1H, d, J_{HP} = 14.3 Hz, CHP), 6.44 (1H, br s, HC=C); δ_C (75 MHz; $CDCl_3$; Me_4Si) 33.60 (*C*H$_2$), 42.33 (d, J_{CP} = 3.5 Hz, *C*H), 54.01 (d, J_{CP} = 5.8 Hz, OCH$_3$), 54.04 (*C*H$_2$N), 54.24 (d, J_{CP} = 6.9 Hz, OCH$_3$), 57.07 (d, J_{CP} = 156.9 Hz, *C*HP), 61.33 (*C*HCl), 68.30 (*C*HOH), 92.69 (C$_q$Cl$_3$), 121.43 (d, J_{CP} = 5.8 Hz, H*C*=C), 137.48 (d, J_{CP} = 3.5 Hz, HC=*C*), 159.24 (C=O); δ_P (121 MHz; $CDCl_3$) 22.06; chromatography R_f 0.20 (EtOAc/PE 3 : 2).

*Dimethyl [2-(2,2,2-trichloroacetyl)-2,3-dihydro-*1H*-isoindol-1-yl] phosphonate (**13**).* (Found: C, 38.8; H, 3.6; N, 3.7. $C_{12}H_{13}Cl_3NO_4P$ requires C, 38.7; H, 3.5; N, 3.8%); ν_{max}(film)/cm^{-1} 1029 (P–O), 1686 (C=O), 3471 (OH); δ_H (300 MHz; $CDCl_3$; Me_4Si) 3.55 (3H, d, J = 11.0 Hz, OCH_3), 3.86 (3H, d, J = 11.0 Hz, OCH_3), 5.09 (1H, dd, J = 14.3 Hz and J = 5.0 Hz, CH_aH_bN), 5.50 (1H, dd, J = 14.3 Hz and J = 6.6 Hz, CH$_a$$H_b$N), 5.88 (1H, d, J_{HP} = 9.4 Hz, CHP), 7.28–7.34 (1H, m, CH_{ar}), 7.35–7.39 (2H, m, CH_{ar}), 7.52–7.58 (1H, m, CH_{ar}); δ_C (75 MHz; $CDCl_3$; Me_4Si) 53.65 (d, J_{CP} = 6.9 Hz, OCH$_3$), 53.86 (d, J_{CP} = 5.8 Hz, OCH$_3$), 54.97 (*C*H$_2$N), 62.03 (d, J_{CP} = 153.5 Hz, *C*HP), 92.77 (C$_q$Cl$_3$), 122.30 (d, J_{CP} = 2.3 Hz, *C*H$_{ar}$), 124.14 (d, J_{CP} = 3.5 Hz, *C*H$_{ar}$), 128.15 (d, J_{CP} = 2.3 Hz, *C*H$_{ar}$), 128.72 (d, J_{CP} = 3.5 Hz, *C*H$_{ar}$), 132.70 (d, J_{CP} = 4.6 Hz, *C*$_{q,ar}$), 137.16 (d, J_{CP} = 5.8 Hz, *C*$_{q,ar}$), 159.38 (*C*=O); δ_P (121 MHz; $CDCl_3$) 21.89; *m*/*z* (ESI) 372/374/376 [M+H]$^+$; chromatography R_f 0.42 (EtOAc/PE 3 : 2).

*Dimethyl (1R,3aR,5S,6S)- and (1S,3aS,5R,6R)-[6-chloro-5-hydroxy-2-(2,2,2-trichloroacetyl)-2,3,3a,4,5,6-hexahydro-*1H*-isoindol-1-yl] phosphonate (**20**).* (Found: C, 33.7; H, 3.7; N, 3.3. $C_{12}H_{16}Cl_4NO_5P$ requires C, 33.8; H, 3.8; N, 3.3%); ν_{max}(film)/cm^{-1} 1047 (P–O), 1255 (P=O), 1649 (C=O), 3473 (OH); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.52 (1H, q, J = 12.1 Hz, CH_aH_b), 2.33 (1H, dt, J = 12.1 Hz en J = 4.1 Hz, CH$_a$$H_b$), 3.08 (1H, br s, O$H$), 3.39–3.56 (1H, m, C$H$), 3.65 (1H, t, J = 9.8 Hz, CH_aH_bN), 3.80 (3H, d, J = 11.0 Hz, OCH_3), 3.83 (3H, d, J = 10.5 Hz, OCH_3), 4.04 (1H, ddd, J = 12.1 Hz, J = 8.0 Hz and J = 4.1 Hz,CHOH), 4.55–4.65 (1H, dd, J = 9.8 Hz and J = 1.7 Hz, CH$_a$$H_b$N), 4.48–4.57 (1H, m, C$H$Cl), 5.07 (1H, d, J_{HP} = 12.1 Hz, CHP), 5.85 (1H, br s, HC=C); δ_C (75 MHz; $CDCl_3$; Me_4Si) 34.75 (*C*H$_2$), 38.87 (*C*H), 53.99 (d, J_{CP} = 6.9 Hz, OCH$_3$), 54.26 (d, J_{CP} = 6.9 Hz, OCH$_3$), 54.68 (*C*H$_2$N), 60.93 (d, J_{CP} = 158.1 Hz, *C*HP), 63.26 (*C*HCl), 68.30 (*C*HOH), 92.73 (C$_q$Cl$_3$), 123.50 (d, J_{CP} = 10.4 Hz, H*C*=C), 136.91 (d, J_{CP} = 6.9 Hz, HC=*C*), 159.32 (C=O); δ_P (121 MHz; $CDCl_3$) 20.46; *m*/*z* (ESI) 426/428/430/432 [M+H]$^+$; mp149–151 °C (from acetone); chromatography R_f 0.12 (EtOAc/PE 2 : 1).

*Dimethyl (1R,3aR,5S,6R)- and (1S,3aS,5R,6S)-[6-chloro-5-hydroxy-2-(2,2,2-trichloroacetyl)-2,3,3a,4,5,6-hexahydro-*1H*-isoindol-1-yl] phosphonate (**21**).* (Found: C, 33.7; H, 3.9; N, 3.3. $C_{12}H_{16}Cl_4NO_5P$ requires C, 33.8; H, 3.8; N, 3.3%); ν_{max}(film)/cm^{-1} 1036 (P–O), 1675 (C=O), 3384 (OH); δ_H (300 MHz; $CDCl_3$; Me_4Si) 1.62 (1H, q, J = 11.4 Hz, CH_aH_b), 2.11 (1H, ddd, J = 11.4 Hz, J = 5.8 Hz and J = 3.3 Hz, CH$_a$$H_b$), 2.33 (1H, d, J = 11.4 Hz, OH), 3.30–3.47 (1H, m, CH), 3.65 (1H, t, J = 9.6 Hz, CH_aH_bN), 3.78 (3H, d, J = 11.0 Hz, OCH_3), 3.82 (3H, d, J = 11.0 Hz, OCH_3), 4.06 (1H, tt, J = 11.4 Hz and J = 3.3 Hz, CHOH), 4.45 (1H, dt, J = 9.6 Hz and J = 1.8 Hz, CH$_a$$H_b$N), 4.80–4.87 (1H, m, C$H$Cl), 5.12 (1H, d, J_{HP} = 12.1 Hz,CHP), 6.03–6.10 (1H, m, HC=C); δ_C (75 MHz; $CDCl_3$; Me_4Si) 30.14 (*C*H$_2$), 39.77 (*C*H), 53.77 (d, J_{CP} = 6.9 Hz, OCH$_3$), 53.87 (d, J_{CP} = 6.9 Hz, OCH$_3$), 54.57 (*C*H$_2$N), 60.64 (d, J_{CP} = 156.9 Hz, *C*HP), 60.73 (d, J_{CP} = 3.5 Hz, *C*HCl), 67.82 (*C*HOH), 92.74 (C$_q$Cl$_3$), 122.37 (d, J_{CP} = 10.4 Hz, H*C*=C), 137.06 (d, J_{CP} = 6.9 Hz, HC=*C*), 159.43 (C=O); δ_P (121 MHz; $CDCl_3$) 21.02; *m*/*z* (ESI) 426/428/430/432 [M+H]$^+$; mp 150–152 °C (from acetone); chromatography R_f 0.05 (EtOAc/PE 2 : 1).

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