Pergamon

Tetrahedron 56 (2000) 4117–4128

TETRAHEDRON

Mechanistic Studies in the Radical Induced DNA Strand Cleavage—Formation and Reactivity of the Radical Cation Intermediate

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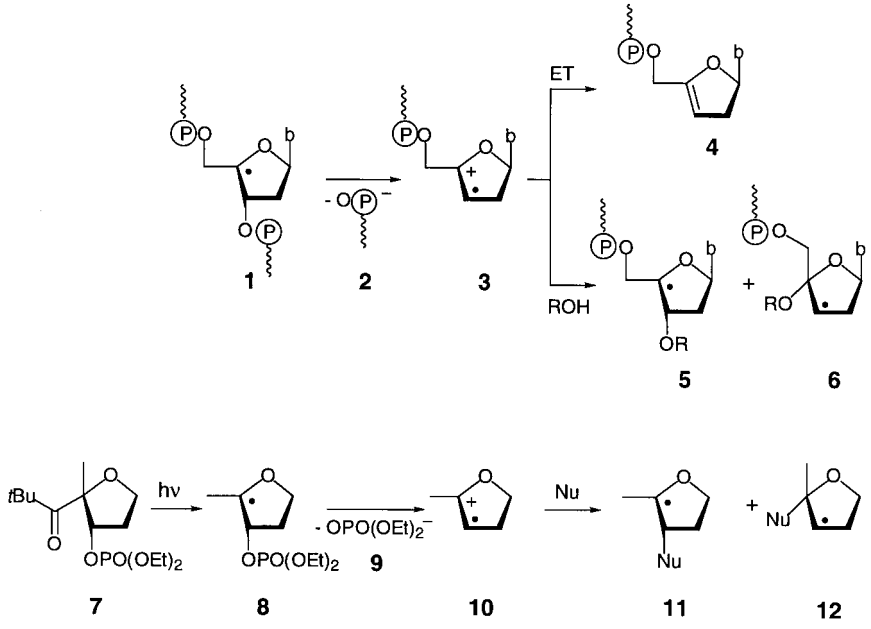
Dedicated to Professor Rolf Huisgen on the occasion of his 80th birthday

Received 22 March 2000; accepted 14 April 2000

Abstract—In order to understand the heterolytic cleavage of 4′-DNA radical **1** and the regioselective attack of nucleophiles at the intermediate DNA radical cation **3**, the chemistry of model radical **8** was studied. It turned out that the heterolytic cleavage in water is favored over homolysis because of the effective solvation of the ions **9** and **10**. The regioselectivity of the nucleophilic attack at radical cation **10** can be explained with the valence bond configuration mixing (VBCM) model. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

The mechanism of the spontaneous cleavage of 4′-DNA radical **1** has been of interest in our laboratory for some time.[1] Schulte-Frohlinde and von Sonntag suggested a heterolytic scission of a 4′-DNA radical **1** forming the phosphorylated strand **2** and the DNA radical cation **3** (Scheme 1).[2]



Scheme 1. General overview of the reaction pathways of C4′-DNA radical and of its model system **8**.

Keywords: 4′-DNA radical; radical cation; regioselective addition; calculations; solvent effect; VBCM.
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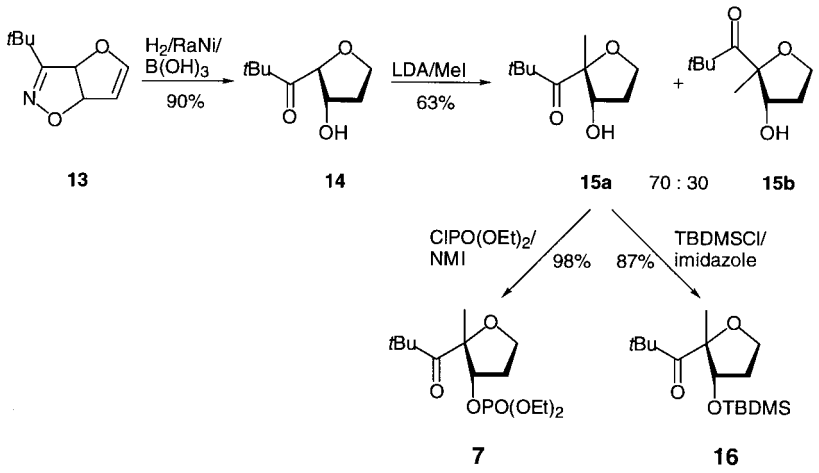


Scheme 2. Synthesis of the radical precursors **7** and **16**.

We have shown that radical cation **3** can be reduced to the corresponding enol ether **4** by electron transfer through DNA[3] or trapped by nucleophilic solvents (H_2O or MeOH) forming the regioisomeric adduct radicals **5** and **6**, with **5** as the major trapping product.[4,5] In this publication, we try to answer the following questions: Why is the phosphate group cleaved heterolytically and not homolytically, and why is the formation of adduct radical **5** preferred over that of adduct radical **6**? We simulated the cleavage of the 4′-DNA radical with model system **8** which is suitable also for theoretical investigations. Radical **8** was generated by photolysis of ketone **7** and studied by electron spin resonance (ESR). In order to answer the first question (heterolysis or homolysis) the thermodynamic aspects of the two cleavage pathways of radical **8** were investigated with quantum chemical calculations and Monte-Carlo solution simulations. To find an answer for the second question (regioselectivity of the nucleophilic attack), trapping experiments of radical cation **10** with different nucleophiles were performed. The experimental observations were then compared with the results of quantum chemical calculations.

Results and Discussion

Synthesis of the radical precursors 7 and 16

The *t*butyl ketones **7** and **16** were synthesized via nitrile oxide cycloaddition to furan starting from 2,2-dimethylpropionaldehyde oxime,[6] subsequent hydrogenation, methylation and separation of the diastereomers **15a** and **15b** by flash chromatography. Silylation and phosphorylation yielded radical precursors **7** and **16** (Scheme 2).

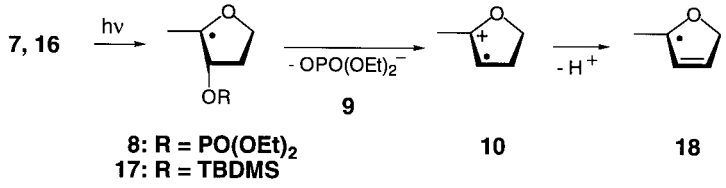
The stereochemistry of the diastereomeric compounds can be assigned by NOE or NOESY experiments and the *cis*-γ-effect.[7]

Generation of radical 8

Photoinduced Norrish Type I cleavage of pivaloyl ketone **7** and subsequent decarbonylation leads to the *t*butyl radical and radical **8**. To study this Norrish Type I cleavage in more detail, ESR measurements were performed with the two precursors **7** and **16** which differ from each other by the substituent at C3 (Scheme 3).

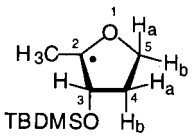
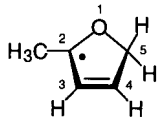
Both precursors were irradiated in benzene solution at 280 K in the cavity of an ESR spectrometer. The photolysis of **16** (R=OTBDMS) resulted in the formation of two radical species. Besides the well known hyperfine coupling pattern of *t*butyl radical,[8] we detected the ESR signal of radical **17**. The *g*-factor of radical **17** is 2.0031 which is a typical value for C2-centered tetrahydofuran-2-yl radicals.[9] The isotropic hyperfine coupling constants and their assignment to the hydrogen atoms of **17** are shown in Table 1. The coupling constants of **17** are very similar to those published by Grossi and coworkers for an analogous radical (SCH_3 instead of OTBDMS, see Table 1).[10] To further ensure the identity of radical **17** and the correct assignment, we calculated the coupling constants of radical **17** (with TMS instead of TBDMS) with the protocol UB3LYP/6-31G*//UHF/3-21G* which produced reliable results for a wide range of organic radicals.[11] The calculated coupling constants are in good agreement with the experimental values (Table 1) and confirm the formation of radical **17** by photolysis of precursor **16**.

When we repeated the experiment with precursor **7**



Scheme 3. Norrish Type I cleavage of pivaloyl ketones **7** and **16**.

Table 1. Experimental and calculated isotropic hyperfine coupling constants (in mT) of radicals **17** and **18**

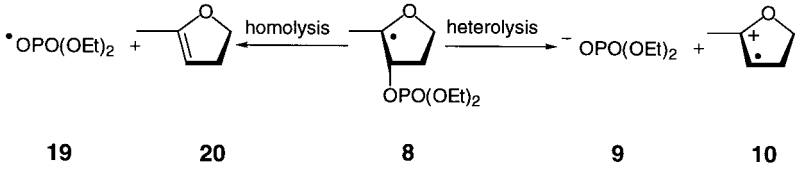
	Exp.	Lit.[a]	Calc.[b]		Exp.	Lit.[c]	Calc.[d]
17				**18**			
Me (3H)	1.96	1.95	1.68	Me (3H)	1.30	1.30	1.31
C3–H (1H)	1.09	1.50	1.15	C3–H (1H)	0.19	0.17	0.35
C4–H_a (1H)	–	–	0.03	C4–H (1H)	1.31	1.37	−1.61
C4–H_b (1H)	–	–	0.04	C5–H (2H)	3.51	3.50	3.32
C5–H_a (1H)	0.13	0.06	0.17				
C5–H_b (1H)	0.31	0.32	0.28				

[a] SMe instead of OTBDMS (see Ref. 10).
[b] TMS instead of TBDMS.
[c] Ref. 10.
[d] Ref. 11.

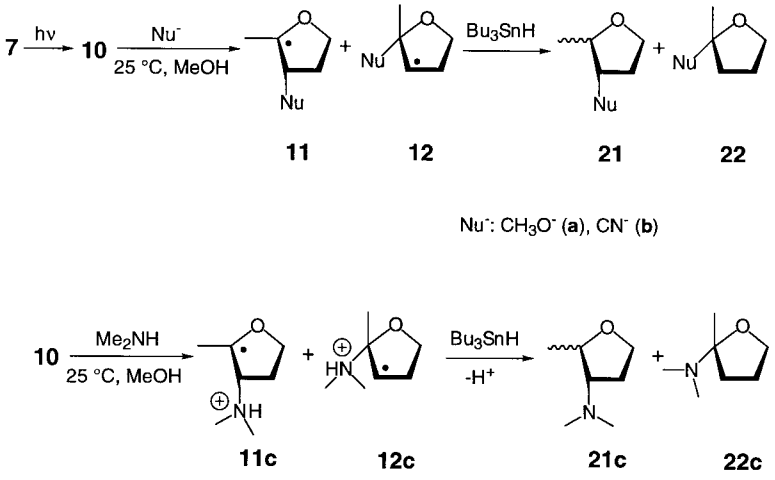
(R=OPO(OEt)$_2$), we detected also two radical species: The ^{t}butyl radical and allyl radical **18** (*g*-factor=2.0029). Allyl radical **18** could be identified due to the results of earlier ESR experiments of Grossi and coworkers in which **18** was generated by an alternative route.[10] In our experiment, allyl radical **18** is formed by elimination of diethyl phosphoric acid from radical **8** that can occur either by a two step mechanism or a concerted mechanism.[12,13] In Scheme 3 the two step mechanism is illustrated for radical **8**. First, heterolytic β-bond cleavage leads to phosphate anion **9** and radical cation **10**.[7] Subsequent deprotonation of radical cation **10** yields allyl radical **18**. Summing up the ESR experiments, we have shown that with precursor **16** (unfavorable leaving group OTBDMS at C3) the direct product of the Norrish Type I cleavage, radical **17**, could be detected. In contrast, with precursor **7** (leaving group OPO(OEt)$_2$ at C3) the elimination product **18** of the initially generated radical **8** was observed.

Heterolytic versus homolytic β-bond cleavage of radical 8

Various experimental studies have shown that the phosphate group in β-(phosphatoxy)radicals is cleaved off heterolytically.[1–5,7,14] The question arises why this β-bond cleavage does not occur homolytically? Motivated by this question, we investigated the thermodynamic aspects for these two cleavage pathways of radical **8**. We calculated the energy differences between the products of the heterolysis



Scheme 4. Possible pathways for β-bond cleavage: homolysis versus heterolysis.



Scheme 5. Reaction of radical cation **10** with the anionic nucleophiles CH_3O^- (**a**) and CN^- (**b**) and the neutral nucleophile dimethylamine (**c**) in the presence of Bu_3SnH.

Table 2. Photolysis of the radical precursor **7** in the presence of different nucleophiles (reaction conditions: conc. **7**=0.018 M^{-1} in methanol, 0.18 M^{-1} nucleophile, 0.18 M^{-1} Bu_3SnH, hν (>280 nm), 25°C, 1 h)

Entry	Nucleophile	Regioselectivity **21**:**22**	*cis*/*trans* ratio of **21**	Yield (%)
a	CH_3O^-	3.5:1	5:1	55
b	CN^-	>50:1	2:1	56
c	Me_2NH	>50:1	100:1	56

(**8**→**9**+**10**) and homolysis (**8**→**19**+**20**) in the gas phase and in water (Scheme 4).

In the gas phase, the formation of charged species is an unfavorable process. Accordingly, ab initio PMP2/6-31+G**//UHF/6-31+G** calculations for the cleavage process of radical **8** predict that the products of the homolysis (**19**+**20**) are 77.6 kcal/mol more stable than those of the heterolysis (**9**+**10**). In solution, the energetic contributions of the solute–solvent interactions have to be taken into account. Therefore, empirical Monte-Carlo simulations[15] were performed to estimate the influence of H_2O as solvent. The results of the simulations show that the ionic products **9**+**10** are stronger solvated by 134 kcal/mol than the neutral products **19**+**20**. By summing up the gas phase energies and the solvation energies of the products, the heterolysis (**8**→**9**+**10**) becomes more favorable by 56.4 kcal/mol in H_2O than the homolytic cleavage (**8**→**19**+**20**). Thus, with radical **8** the heterolytic cleavage is favored over homolysis because of the effective solvation of the ionic products **9**+**10**.

Regioselectivity of the nucleophilic attack

Radical cations are known to undergo a variety of reactions, such as addition of nucleophiles, reduction by electron transfer, carbon–carbon bond cleavage and deprotonation reactions.[16–20] We focused our attention on the nucleophilic trapping reaction. In order to elucidate the trapping regioselectivity of radical cation **10** as a function of the nucleophile, the precursor **7** was irradiated in the presence of sodium methoxide, potassium cyanide, or dimethylamine. The intermediate radicals **11** and **12**, formed after addition of the anionic nucleophiles, were quenched with Bu_3SnH yielding the products **21** (C3 addition) and **22** (C2 addition) (Scheme 5). The reaction of radical cation **10** with dimethylamine is slightly more complex because the initially formed addition products **11c** and **12c** have to abstract a hydrogen atom and to donate a proton in order to form the neutral products **21c** and **22c**.

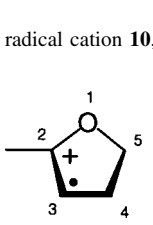
The experimental results are summarized in Table 2. Only the C3 addition product **21** was detected in the reactions of cyanide and dimethylamine, while both regioisomers were formed in the reaction with methoxide in a ratio of **21**:**22**=3.5:1. This regioselectivity is similar to that observed by Arnold[16] and Roth[20] for alkene radical cation reactions with nucleophiles.

Regioisomer **21** can be formed as *cis* or *trans* diastereoisomer. With all three nucleophiles the *cis* isomer of product **21** was formed in excess because the substituent (Nu) in radical **11** induces a *trans*-attack of the H-donor Bu_3SnH.[21] As expected, the *cis*–*trans* ratio of the diastereoisomers increased with increasing bulk of the substituent from 2:1 (Nu=CN) via 5:1 (Nu=OCH_3) to 100:1 (Nu=NMe_2).

At first glance one might expect the regioselectivity of the nucleophilic attack at **10** to be determined through electrostatic effects as well as frontier orbital interactions. In the former case, the center of positive charge in **10** will be attacked preferentially while in the latter case the center of largest LUMO coefficient will be the most reactive. In order to evaluate these possibilities, radical cation **10** was optimized at the BHLYP/6-31+G(d,p) level of theory. Using this geometry the charge and spin density distribution as well as the LUMO coefficients was analyzed at the BHLYP/6-31G(d,p) level of theory for the carbon atoms C2 and C3 as well as the ring oxygen atom (Table 3).

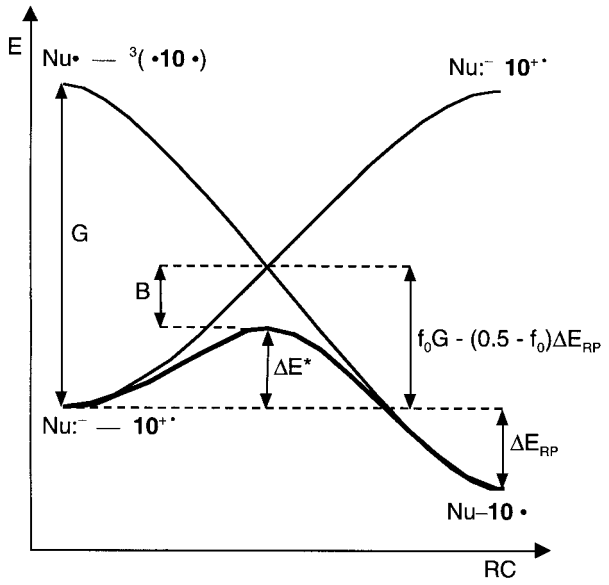
Most of the positive charge is located at carbon atom C2 while the spin density is mainly located at C3 and O1. This implies that electrostatic interactions will guide

Table 3. Spin densities, atomic charges, and LUMO coefficients for radical cation **10**, and spin densities for the corresponding neutral triplet (BHLYP/6-31G(d,p)//BHLYP/6-31+G(d,p) values)



10

	Radical cation			Neutral triplet
Position	Spin density	Atomic charge	LUMO coefficient	Spin density
O1	0.20	−0.26	−0.23	0.17
C2	0.02	+0.56	+0.53	0.83
C3	0.81	−0.06	−0.35	1.06



Scheme 6. Valence bond configuration mixing (VBCM) diagram for the addition of nucleophiles to radical cation **10**.

nucleophilic attack into the C2 position. Assuming HOMO(nucelophile)–LUMO(radical cation) interactions to be dominant, leads to a similar result: the LUMO coefficient is significantly larger at C2 (+0.53) than at C3 (−0.35). Taken together we have to recognize that neither FMO nor electrostatic arguments give any indication for the preferential formation of the C3 addition products.

Recently the regioselectivity observed in nucleophilic addition reactions to radical cations of heterocyclic aromatic compounds has been studied using the valence bond configuration mixing (VBCM) model.[22,23] The VBCM model assumes the reaction barrier to be the result of the crossing of the reactant and product state curves (Scheme 6).

The reactant state refers to the separate reactants at infinite separation. The product state is described by a newly formed polar covalent bond between the nucleophile and the alkene radical cation. Formally this state derives from the reactant state through: (i) one electron oxidation of the nucleophile; (ii) one electron reduction of the radical cation to yield the neutral alkene; and (iii) unpairing of the newly formed alkene π-bond. This latter step can be approximated by assuming conversion to the triplet state. The energetic demand for all three steps are usually summed up in one excitation energy factor G (Scheme 6). What fraction f_0 of the initial gap G enters into the barrier depends on the steepness of the state curves, steeper curves leading to smaller factors f_0 and smaller barriers. As usual,[22,23] the factor f_0 integrates the steepness of the reactant and product curves into an effective parameter. The transition state for the reaction is located below the actual curve crossing point, the energy difference being defined by the transition state resonance energy B. Finally, the reaction barrier ΔE^* is also influenced by the reaction exothermicity ΔE_{RP}. An approximate equation[22] integrating all four factors is thus:

$$\Delta E^* = f_0 G + (0.5 - f_0)\Delta E_{RP} - B \quad (1)$$

Assuming Eq. (1) to be applicable for addition to the C2 as well as the C3 position in **10**, we can express the regioselectivity for nucleophilic addition as a combination of three reactivity factors $\Delta\Delta E(f)$, $\Delta\Delta E(\Delta E_{RP})$, and $\Delta\Delta E(B)$:

$$\Delta\Delta E^*(\text{C2–C3}) = \Delta\Delta E(f) + \Delta\Delta E(\Delta E_{RP}) - \Delta\Delta E(B) \quad (2)$$

$$\Delta\Delta E(f) = (f_0^{C2} - f_0^{C3})G \quad (3)$$

$$\Delta\Delta(\Delta E_{RP}) = [(0.5 - f_0^{C2})\Delta E_{RP}^{C2} - (0.5 - f_0^{C3})\Delta E_{RP}^{C3}] \quad (4)$$

$$\Delta\Delta E(B) = (B^{C2} - B^{C3}) \quad (5)$$

All factors leading to negative values of $\Delta\Delta E^*$(C2–C3) reflect preferential formation of the C3 addition product **11**. As outlined before[22] the first of these factors $\Delta\Delta E(f)$ can be correlated with the spin density at C2 and C3 after one electron reduction and excitation to the triplet state. The f_0 factors will be smaller, hence the reaction barrier lower for the position of higher spin density. According to the triplet spin densities calculated at the BHLYP/6-31G(d,p)//BHLYP/6-31+G(d,p) level of theory (Table 3) the C3 position is slightly more reactive than the C2 position. The difference between these two centers appears to derive from the fact that some of the spin density is also

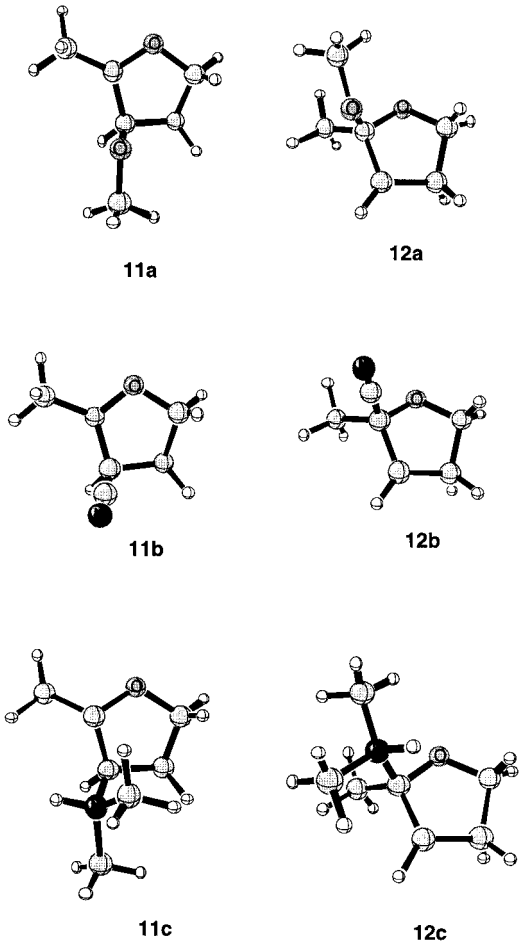


Figure 1. Structures of the C3-addition products **11** and the C2-addition products **12** formed through reaction of radical cation **10** with (**a**) methoxide, (**b**) cyanide and (**c**) dimethylamine. Only the most favorable conformations for each product are shown.

Table 4. Absolute and relative reaction energies (all energies are in kcal/mol) (in parenthesis) for the gas phase reaction of **10** with (**a**) methoxide, (**b**) cyanide, and (**c**) dimethylamine [BHLYP/6-31+G(d,p) level of theory]

Nucleophile	System	ΔE_{tot}	ΔH^{298}	ΔG^{298}	$\Delta G(SP)^{298}$
CH_3O^-	**11a** (C3)	−173.7 (+0.5)	−168.9 (+1.5)	−156.7 (+1.0)	−154.8 (+0.7)
	12a (C2)	−174.2 (0.0)	−170.4 (0.0)	−157.7 (0.0)	−155.5 (0.0)
CN^-	**11b** (C3)	−148.0 (0.0)	−145.4 (0.0)	−127.1 (0.0)	−133.5 (0.0)
	12b (C2)	−140.5 (+7.5)	−139.0 (+6.4)	−133.6 (+6.5)	−126.8 (+6.7)
$HNMe_2$	**11c** (C3)	−19.8 (+0.3)	−15.8 (+1.2)	−1.9 (+0.8)	−2.8 (+0.2)
	12c (C2)	−20.1 (0.0)	−17.0 (0.0)	−2.7 (0.0)	−3.0 (0.0)

located on the ring oxygen atom adjacent to C2 and that this delocalization reduces the C2 spin density. The difference ($f_0^{C2}-f_0^{C3}$) is solely dependent on the characteristics of the radical cation and thus independent of the nucleophile. We may therefore conclude that the reactivity factor $\Delta\Delta E(f)$ points to preferred addition to C3 of radical cation **10** for all nucleophiles. The difference in resonance energies $\Delta\Delta E(B)$ has been shown to be dependent on the LUMO coefficients of radical cation **10**.[22] Using the data given in Table 3 we see that addition to the C2 position is preferred in this case. Again, this argument is solely dependent on the characteristics of radical cation **10** and thus independent of the choice of nucleophile. Considering only the reactivity factors $\Delta\Delta E(f)$ and $\Delta\Delta E(B)$, we must conclude that no clear preference exists for addition to either the C2 or the C3 position in radical cation **10**. This conclusions also suggests that the third reactivity factor $\Delta\Delta E(\Delta E_{RP})$ might be mainly responsible for the observed regioselectivities. Under the condition that the f_0 factors are smaller than 0.5, Eq. (4) implies that formation of the more stable regioisomer will be accompanied by a lower reaction barrier. The magnitude of $\Delta\Delta E(\Delta E_{RP})$ depends directly on the relative stability of the C3 and C2 addition products **11** and **12**, respectively. We therefore studied the addition products obtained from reaction of **10** with (**a**) methoxide, (**b**) cyanide, and (**c**) dimethylamine at the BHLYP/6-31+G(d,p) level of theory. The structures of the C2 and C3 addition products for these three nucleophiles are shown in Fig. 1 (only the energetically most favorable conformations are shown), and the absolute and relative reaction energies for the addition reaction have been collected in Table 4.

Formation of the C2 addition products is slightly preferred for the nucleophiles methoxide and dimethylamine while cyanide strongly prefers addition to the C3 position in the gas phase. This conclusion does not depend on whether energies, enthalpies or free enthalpies are considered. Combination of single point energies calculated at the BHLYP/aug-cc-pVDZ//BHLYP/6-31+G(d,p) level and addition of the BHLYP/6-31*G(d,p) thermochemical corrections gives slightly different free enthalpies $\Delta G(SP)^{298}$. These differ, however, only marginally from the free enthalpy differences calculated at the BHLYP/6-31*G(d,p) level (Table 4). Single point calculations using the even larger aug-cc-pVTZ basis set were performed for the dimethylamine adducts **11c** and **12c**, but the relative energy changes not significantly. It decreases by only 0.2 kcal/mol so that **11c** and **12c** become equal in energy. This indicates that the BHLYP/aug-cc-pVDZ single point energies are sufficiently accurate for the present purpose.

We can thus conclude that gas phase calculations predict the C2 and C3 addition products of methoxide and dimethylamine to be of similar stability while a clear preference for C3 addition is predicted for cyanide. This result can be understood on the basis of two electronic effects: (a) radical stability and (b) anomeric effects. With focus on the local environment of the radical center the C3 addition products are tertiary alkyl radicals with additional stabilization through the ring oxygen atom while the C2 addition products are secondary alkyl radicals. Depending on the nucleophile of choice, the C2 addition products might, however, be stabilized through anomeric and exoanomeric effects. The preferred conformer found for **12a** does indeed allow for both stereoelectronic effects to be present. We might, however, also consider the much lower dipole moments of the C2 addition products **12a** and **12c** to be the source of stabilization relative to the corresponding C3 addition products. This type of stabilization appears to be unavailable for cyanide addition product **12b**. The different dipole moments calculated in the gas phase (Table 5) also suggest that solvent effects will lead to significant changes in the relative energies between C2/C3 regioisomers.

The PCM continuum solvation method[24] was used to explore the different solvation free enthalpies for the gas phase structures shown in Fig. 1 in methanol (ϵ=32.6).

Table 5. Gas phase dipole moments and relative free enthalpies (all energies are in kcal/mol) in methanol solution for the addition products formed in the reaction of **10** with (**a**) methoxide, (**b**) cyanide, and (**c**) dimethylamine [PCM/BHLYP/6-31+G(d,p)//BHLYP/6-31+G(d,p)]

Nucleophile	System	μ [D]	$\Delta\Delta G298$ (SP) (in MeOH)	$\Delta\Delta G298$ (in MeOH)
CH_3O^-	**11a** (C3)	2.6	+0.3	+0.3
	12a (C2)	0.6	0.0	0.0
CN^-	**11b** (C3)	3.7	0.0	0.0
	12b (C2)	4.4	+7.0	+6.9
$HNMe_2$	**11c** (C3)	5.8	0.0	0.0
	12c (C2)	3.5	+5.4	+5.3

The resulting differences in free enthalpies of solvation ΔG_{solv} were combined with the gas phase free enthalpy differences $\Delta G(SP)^{298}$ from Table 4 to obtain an estimate for the free enthalpy differences $\Delta\Delta G^{298}(SP)$ in methanol solution at 298 K (Table 5). Addition of the two ionic nucleophiles methoxide and cyanide appears to proceed with similar regioselectivity in the gas phase and in methanol solution. The situation is, however, considerably different for addition of dimethylamine. In this latter case, the C3 addition product **11c** is better solvated than **12c** by more than 5 kcal/mol, leading to a completely different relative product stability in solution than in the gas phase. In how far these large differences in free energy of solvation are due to the use of gas phase structures was probed by reoptimization of all structures shown in Fig. 1 in the presence of the PCM solvent model. Only small structural relaxation can be noted under these conditions and the calculated free energy differences $\Delta\Delta G^{298}$ using relaxed structures are quite close to those calculated for the gas phase structures (Table 5). Considering the predicted differences in reaction energies in Table 5, we can therefore conclude that the third reactivity factor $\Delta\Delta E(\Delta E_{RP})$ is favorable for C3 addition of cyanide and dimethylamine, while no clear regiochemical preference exists for addition of methoxide. Gratifyingly, the experimentally observed regioselectivities are not too far from what would be predicted from consideration of the product stabilities alone. This implies that the influence of the other two reactivity factors $\Delta\Delta E(f)$ and $\Delta\Delta E(B)$ cannot be too large in addition reactions to radical cation **10**.

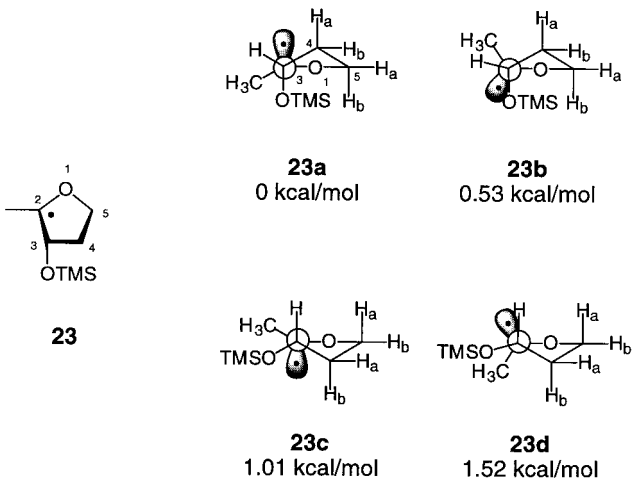
Conclusion

Generation of the tetrahydrofuran-2-yl radical **8** through photoinduced Norrish I cleavage is rapidly followed by heterolytic elimination of phosphate (**8→10**). In benzene as solvent, deprotonation of radical cation **10** yields the corresponding allyl radical **18**. Using the unfavorable leaving group TBDMSO as β-substituent no elimination can be observed. Calculations show that in the gas phase the heterolytic elimination process is strongly disfavored in comparison to the homolytic β-bond cleavage, whereas in polar solution the heterolysis dominates over homolysis due to the effective solvation of the charged products of the heterolysis. The radical cation **10** formed in the heterolysis was trapped by anionic as well as neutral nucleophiles. The regioselectivities observed in the trapping step are not in agreement with the charge distribution in radical cation **10**, but mainly reflect the stabilities of the primary addition products.

Computational procedures

Quantum chemical calculations

All ab initio and DFT calculations were carried out with the program GAUSSIAN94 and GAUSSIAN98.[25] For the calculation of the isotropic hyperfine coupling constants of radical **17**, we replaced the TBDMS group by a TMS (see radical **23**, Scheme 7). In order to take into account the flexibility of the ring system, the coupling constants of four different ring conformers of radical **23** were calculated with the method UB3LYP/6-31G(d)//UHF/3-21G(d).[11] Scheme 7 shows these four conformers **23a**–**d** in a Newman projection along the C3–C2 bond. Additionally the relative UB3LYP/6-31G(d)//UHF/3-21G(d) energies are listed below. The lowest energy is found for the conformer **23a** which profits from a stabilizing interaction of the single occupied molecular orbital (SOMO) with the σ*-orbital of the C3–O bond. The least stable conformer is **23d** with eclipsed methyl and OTMS group. Finally, the isotropic hyperfine coupling constants given in Table 1 were calculated by averaging over all four conformers. The contribution of each conformer to the mean value was determined with a Boltzmann distribution using the relative UB3LYP/6-31G(d)//UHF/3-21G(d) energies.



Scheme 7. Conformers for the calculation of the isotropic hyperfine coupling constants of radical **23**.

For the calculation of the gas phase energy difference between the products of the heterolysis (**9**+**10**) and homolysis (**19**+**20**), the ethyl groups in the phosphate moieties were replaced by methyl groups to save computational time. All products were fully optimized on the unrestricted Hartree–Fock level with the basis set 6-31+G(d,p). The gas phase energies were determined by single point, spin projected[26] Møller-Plesset second order perturbation calculations[27] using the basis set 6-31+G(d,p). The atomic charges were calculated with the CHELPG procedure.[28]

The reaction of radical cation **10** with methoxide, cyanide, and dimethylamine has been studied using the hybrid density functional BHandHLYP[29] in combination with the 6-31+G(d,p) basis set. This method has been used successfully before in studies of alkene radical cations with nucleophiles and will be designated 'BHLYP/6-31+G(d,p)'.[30] Using these geometries single point energies have been calculated with the same density functional but the slightly larger aug-cc-pVDZ and, in part, aug-cc-pVTZ basis sets.[31] Due to known problems with diffuse basis functions, the spin and charge distribution as well as the LUMO coefficients have been calculated at the BHLYP/6-31G(d,p)//BHLYP/6-31+G(d,p) level of theory. Atomic charges have been obtained by fitting the molecular

electrostatic potential using the CHELPG procedure. The LUMO coefficients refer to the 2PZ component of the 6-31G split valence basis set. Using the 3PZ coefficients, the same trends are observed.

Monte-Carlo solution simulations

The simulations were carried out with the program BOSS 3.4.[32] The solvent was represented by a cubic box (side length=25 Å) containing 512 TIP4P water molecules at 298 K and 1 atm. Free energies of solvation changes were calculated for the interconversions of **10** to **13** and **9** to **14** (with methyl instead of ethyl in the phosphate moieties). The mutations took place within 20 steps by gradually converting the UHF/6-31+G(d,p) optimized geometries, the UMP2/6-31+G(d,p)//UHF/6-31+G(d,p) atomic CHELPG charges (see above) and the standard Lennard–Jones parameters into each other. Each step consisted of 2×10^6 configurations for equilibration followed by 4×10^6 configurations for averaging.

Experimental

General experimental information

All reagents are commercially available from Fluka Chemie Co. and Aldrich Chemical Co. and used without further purification. Et_2O and THF were distilled from NaH. All temperatures and boiling points (bp) are uncorrected. The reactions were carried out under argon (Ar) with the exclusion of moisture. Flash-chromatography was conducted with silica gel C 560 KV of Chemische Fabrik Uetikon and silica gel 60 of Merck Co using the indicated and freshly distilled solvents. NMR spectra: Varian Gemini 300 or Bruker AMX 400 (^{1}H, ^{13}C and ^{31}P with tetramethysilane, chloroform-d_3 as internal and triphenyl phosphate (-18) as external standard; relative stereochemistry by NOEDIF or NOESY experiments). ESR spectra: Bruker ESP-300. IR spectra: Perkin–Elmer 1600 Series FT-IR. MS: VG 70-250 (for FAB with 3-nitrobenzyl alcohol as matrix), Finnigan MAT 312 or Hewlett–Packard 5890 Series; GC/MS using a Hewlett–Packard 5970A or 5971 mass selective detector. UV/VIS-spectrometer: Perkin–Elmer Lamda II. Photolysis: Oriel 68810 with Osram 500 W mercury arc high-pressure lamp in combination with a 280 nm cut-off filter. For in situ generation of the radicals observed during ESR measurements: Hanovia 977-B1 (1000 W) Hg–Xe high pressure lamp with a water cooled IR-Filter UG-5 of Schott.

General procedure for photolysis of precursors 7 and 16

A solution of 10–20 mg of the precursor **7** or **16** in 3 ml MeOH was deoxygenated in a quartz-cuvette by bubbling argon through it for 15 min. Undecane as internal standard, a 10-fold excess of tributyltinhydride as H-donor and a 10-fold excess of the desired nucleophile was added. Irradiations were carried out for 1 h at 25°C using an Osram high-pressure mercury arc lamp (500 W, 280 nm cut-off filter). The irradiation mixtures were analyzed and identified without work-up directly by GC with the synthesized or commercially available references and quantified using internal calibration.

General procedure for ESR measurements of precursors 7 and 16

In a typical experiment ~150 mg of the precursor were dissolved in benzene (1 ml). The resulting solution was deoxygenated by bubbling argon through the solution for 15 min. After sealing the quartz tube, the sample was cooled down to 280 K in the ESR probe head and irradiated using the Hg–Xe high-pressure lamp of Hanovia. The in situ formed radicals were identified directly by the resulting ESR spectra. The *g*-factor of the ^{t}butyl radical (2.0028)[8] was used as internal reference to determine the *g*-factors of radicals **17** and **18**.

Synthesis of the radical precursor

2,2-Dimethyl-propionaldehyde oxime. To a solution of pivalaldehyde (50.0 g, 580 mmol) in 1/1 EtOH/H_2O (240 ml) with ice (250 g) and $NH_2OH\cdot HCl$ (44.3 g, 638 mmol) NaOH (58.0 g, 1.45 mol) as a 50% solution and ice alternatively were added in order to keep the temperature at 25°C. After stirring for 2 h the reaction mixture was extracted with Et_2O (1×500 ml). The cooled aqueous phase was neutralized with conc. HCl and extracted with Et_2O (2×500 ml). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo yielding the oxime (38.6 g, 66%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.36 (s, 1H), 1.11 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.1, 33.6, 27.3; IR (KBr) 3329, 2964, 1872, 1702, 1648, 1463, 1391, 1366, 1305, 1206, 948 cm^{-1}; MS (EI) *m/z* 86, 85, 84, 73, 69, 68, 58, 57, 56, 55, 53, 52, 51, 50, 44, 43, 42, 41. Anal. Calcd for $C_5H_{11}NO$ [101.15]: C, 59.37; H, 10.96; N, 13.85; O, 15.82. Found: C, 59.12; H, 11.21; N, 13.73; O, 15.75.

1-Chloro-2,2-dimethyl-propan-1-one oxime. To a solution of 2,2-dimethylpropionaldehyde oxime (32.7 g, 323 mmol) in dry DMF (250 ml) was added 1/6 (~8 g) of the amount of *N*-chlorosuccinimide (46.2 g, 339 mmol). HCl as gas (~20 ml) was bubbled through the solution to initiate the reaction indicated by the arising blue color of the solution. The rest of the succinimide was added in portions with intermediate cooling to keep the temperature below 35°C. After stirring for 2 h the reaction mixture was poured on ice water (700 ml) and the aqueous phase was extracted with Et_2O (2×350 ml). After washing with H_2O (1×600 ml) the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo yielding the hydroxy iminoylchloride (41.8 g, 95%) as a pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.23 (s, 1H), 1.27 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 150.0, 39.8, 27.8; IR (KCl) 3329, 2976, 1622, 1480, 1461, 1427, 1396, 1366, 1254, 1045, 1009, 973 cm^{-1}; MS (EI) *m/z* 100, 99, 84, 69, 68, 67, 57, 56, 55, 54, 53, 52, 51, 50, 49, 43, 42, 41. Anal. Calcd for $C_5H_{10}ClNO$ [135.59]: C, 44.29; H, 7.43; N, 10.33; O, 11.80. Found: C, 45.30; H, 7.81; N, 10.07; O, 12.63.

3-*tert*-Butyl-3a,6a-dihydrofuro[2,3-]isoxazole (13). To a solution of 1-chloro-2,2-dimethyl-propan-1-one oxime (17.0 g, 125 mmol) in furan (1000 ml) was added over a

period of 26 h by a syringe pump NEt_3 (25.4 g, 251 mmol) in furan (60 ml). After the completed addition and stirring for additional three days by total enclosure of light the reaction mixture was concentrated in vacuo. The residue was dissolved in Et_2O (750 ml) and washed with sat. $NaHCO_3$ solution (1×750 ml). After extracting the aqueous phase with Et_2O (2×750 ml) the organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (Uetikon, pentane/^{t}butylmethyl ether 20/1→10/1) giving compound **13** (8.90 g, 43%) as a colorless solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (dt, J=3.1, 0.7 Hz, 1H), 5.84 (d, J=8.8 Hz, 1H), 5.76 (ddd, J=8.8, 2.5, 1.1 Hz, 1H), 5.31 (t, J=2.6 Hz, 1H); 1.29 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 162.3, 148.6, 101.2, 89.5, 86.8, 33.1, 29.0; IR (KBr) 3100, 2970, 2907, 2872, 1607, 1480, 1463, 1397, 1366, 1352, 1283, 1247, 1221, 1204, 1142, 1054, 1030, 1017, 980, 937, 918, 891, 864, 826, 802, 725 cm^{-1}; MS (EI) m/z 167 (M^+), 152, 124, 111, 109, 107, 95, 91, 81, 79, 77, 69, 68, 67, 65, 57, 56, 55, 53, 52, 51, 41. Anal. Calcd for $C_9H_{13}NO_2$ [167.21]: C, 64.65; H, 7.84; N, 8.38; O, 19.14. Found: C, 64.73; H, 7.65; N, 8.36; O, 19.14.

(2*R)-*tert*-Butylcarbonyl-(3*S**)-hydroxytetrahydrofuran (14).** To a stirred solution of compound **13** (4.50 g, 26.9 mmol) in 5/1 MeOH/H_2O (90 ml) boric acid (5.02 g, 80.7 mmol) and five spatula tips of W-2 RaNi, previously activated by washing with H_2O (10×) and MeOH (5×), were added. After exchanging the Ar- by a H_2 atmosphere and stirring for 19 h the reaction mixture was filtered through Celite. The Celite was washed extensively with MeOH and the collected filtrate was concentrated in vacuo to the volume of the H_2O. After adding H_2O (100 ml) with NaCl (10 g) the aqueous phase was extracted with CH_2Cl_2 (3×250 ml). The combined organic layers were decolorized by activated carbon, dried by $MgSO_4$ and concentrated in vacuo yielding compound **14** (4.19 g, 90%) as a pale yellow solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.68–4.61 (m, 2H), 4.17 (dt, J=8.7, 6.7 Hz, 1H), 3.94 (td, J=8.4, 3.9 Hz, 1H), 2.47 (d, J=5.8 Hz, 1H), 2.16 (dtd, J=13.6, 8.7, 5.0 Hz, 1H), 2.03 (dddd, J=13.1, 6.7, 3.9, 1.6 Hz, 1H), 1.22 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 214.4, 84.0, 73.5, 67.2, 44.0, 35.6, 25.7; IR (KBr) 3438, 2970, 2873, 1710, 1479, 1393, 1367, 1325, 1292, 1229, 1184, 1112, 1054, 1023, 1004, 921, 898, 872, 852, 816 cm^{-1}; MS (EI) m/z 157, 144, 116, 101, 88, 87, 86, 85, 71, 70, 69, 59, 58, 57, 56, 55, 45, 43, 42, 41. Anal. Calcd for $C_9H_{16}O_3$ [172.22]: C, 62.77; H, 9.36; O, 27.87. Found: C, 62.60; H, 9.28; O, 27.98.

(2*R)-*tert*-Butylcarbonyl-(3*S**)-hydroxy-(2*R**)-methyltetrahydrofuran (15a) and (2*S**)-*tert*-butylcarbonyl-(3*S**)-hydroxy-(2*S**)-methyltetrahydrofuran (15b).** To a solution of **14** (6.13 g, 35.6 mmol) in dry THF (250 ml) was added at −78°C a 1.5 M LDA solution (83.1 ml, 124.6 mmol). The resulting mixture was stirred for 15 min at −78°C and for 2.5 h at 25°C. After the deprotonation the mixture was cooled again to −78°C and MeI (50.5 g, 356 mmol) was added. Stirring for 3 h at −78°C the mixture was allowed to warm up to 25°C slowly overnight using intermediately an ice bath. After 17 h the suspension was quenched with sat. NH_4Cl solution (200 ml) and poured in a 10% $Na_2S_2O_3$ solution (400 ml). The aqueous solution was extracted with Et_2O (3×750 ml) and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The diastereomers were separated and purified by chromatography (Merck, toluene/acetone 40/1→20/1) giving compound **15a** (2.83 g, 43%) and **15b** (1.34 g, 20%) as colorless oils: **15a:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31 (ddd, J=4.8, 3.3, 1.4 Hz, 1H), 4.17 (ddd, J=10.8, 8.1, 5.9 Hz, 1H), 4.08 (td, J=8.3, 2.2 Hz, 1H), 3.03 (dd, J=3.2, 1.7 Hz, 1H), 2.22–2.09 (m, 1H), 1.94 (dddd, J=13.1, 6.0, 2.3, 1.2 Hz, 1H), 1.28 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 220.3, 95.5, 78.6, 67.4, 45.4, 32.3, 26.1, 25.8; IR (NaCl) 3492, 2973, 2880, 1687, 1483, 1456, 1391, 1365, 1315, 1294, 1220, 1179, 1146, 1117, 1091, 1049, 1035, 985 cm^{-1} MS (EI) m/z 186 (M^+), 171, 129, 102, 101, 87, 85, 84, 83, 73, 71, 69, 59, 58, 57, 56, 55, 53, 45, 44, 43, 42, 41. Anal. Calcd for $C_{10}H_{18}O_3$ [186.25]: C, 64.49; H, 9.74; O, 25.77. Found: C, 64.26; H, 9.73; O, 25.69. **15b:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.30 (td, J=7.0, 3.0 Hz, 1H), 4.02 (td, J=8.3, 5.6 Hz, 1H), 3.89 (dt, J=8.6, 7.4 Hz, 1H), 2.91 (d, J=3.1 Hz, 1H), 2.15–2.04 (m, 1H), 1.95 (ddd, J=15.4, 12.5, 4 Hz, 1H), 1.31 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 220.8, 90.7, 75.8, 64.6, 45.0, 31.7, 26.1, 20.5; IR (NaCl) 3456, 2956, 2875, 1691, 1483, 1451, 1391, 1365, 1202, 1175, 1121, 1101, 1041, 992 cm^{-1}; MS (EI) m/z 171, 153, 129, 115, 102, 101, 85, 83, 73, 71, 69, 59, 58, 57, 56, 55, 53, 45, 44, 43, 42, 41. Anal. Calcd for $C_{10}H_{18}O_3$ [186.25]: C, 64.49; H, 9.74. Found: C, 64.66; H, 9.86. The relative stereochemistry of **15a** and **15b** was determined by NOESY experiments.

(2*R)-*tert*-Butylcarbonyl-(3*S**)-diethylphosphoryloxy-(2*R**)-methyltetrahydrofuran (7).** Furanol **15a** (960 mg, 5.15 mmol) in dry CH_2Cl_2 (20 ml) was cooled to 0°C followed by addition of *N*-methyl imidazole (5.08 g, 61.9 mmol) and $ClPO(OEt)_2$ (4.63 g, 25.8 mmol). After stirring for 15 min at 0°C and 15 h at 25°C the reaction mixture was diluted with CH_2Cl_2 (80 ml) and washed with 30% tartaric acid solution (1×100 ml). The aqueous phase was extracted with Et_2O (3×150 ml) and the organic layers were combined and washed successively with sat. $NaHCO_3$ (1×400 ml) and H_2O (1×400 ml). After drying over $MgSO_4$ and concentrating in vacuo the residue was purified by chromatography (Merck, pentane/acetone 10/1→5/1) yielding the phosphate **7** (1.62 g, 98%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.87 (dd, J=4.6, 4.5 Hz, 1H), 4.19–4.00 (m, 6H), 2.36–2.22 (m, 2H), 1.36–1.30 (m, 6H), 1.31 (s, 3H), 1.22 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 215.1, 94.0 (d, J=9.5 Hz), 84.1 (d, J=5.6 Hz), 66.8, 63.7 (d, J=6.0 Hz), 63.6 (d, J=6.0 Hz), 45.1, 31.7, 26.1, 25.7, 16.0 (d, J=7.2 Hz); ^{31}P NMR (121 MHz, $CDCl_3$) δ −3.18 (sext, J=7.2 Hz); IR (NaCl) 2979, 2934, 1699, 1482, 1445, 1392, 1368, 1268, 1154, 1102, 1036, 930 cm^{-1}; MS (EI) m/z 323 ($M+H^+$), 237, 156, 155, 138, 127, 109, 99, 84, 83, 82, 81, 69, 57, 55, 53, 43, 41. Anal. Calcd for $C_{14}H_{27}O_6P$ [322.34]: C, 52.17; H, 8.44; O, 29.78. Found: C, 52.12; H, 8.53; O, 29.91.

(2*R)-*tert*-Butylcarbonyl-(3*S**)-*tert*-butyldimethyl-silyloxy-(2*R**)-methyltetrahydrofuran (16).** To a solution of **15a** (500 mg, 2.69 mmol) in dry DMF (5 ml) were added imidazole (1.84 g, 26.8 mmol) and TBDMSCl (2.09 g, 13.4 mmol). After stirring for 19 h MeOH (5 ml) was added and the reaction mixture was poured on H_2O (100 ml). The aqueous phase was extracted with Et_2O (3×100 ml)

and the combined organic layers were washed with H_2O (2×250 ml). After drying over $MgSO_4$ and concentrating in vacuo the residue was purified by chromatography (Merck, pentane/Et_2O 1/0→40/1) yielding the silylether **16** (704 mg, 87%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.25 (d, J=3.8 Hz, 1H), 4.14 (ddd, J=11.3, 7.8, 5.6 Hz, 1H), 4.06 (tdd, J=8.2, 1.7, 0.6 Hz, 1H), 2.16–2.04 (m, 1H), 1.81–1.75 (m, 1H), 1.25 (s, 3H), 1.20 (d, J= 0.6 Hz, 9H), 0.84 (d, J=0.6 Hz, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 216.6, 95.4, 79.9, 67.3, 45.1, 34.2, 27.0, 25.9, 25.8, 18.0, −4.8, −5.2; IR (NaCl) 2954, 2931, 2882, 2858, 1699, 1483, 1472, 1462, 1390, 1364, 1272, 1188, 1117, 1098, 1054, 1030, 1002, 987, 922, 836, 777 cm^{-1}; MS (EI) *m/z* 301 (M+H$^+$), 285, 243, 216, 215, 187, 171, 159, 157, 143, 131, 129, 115, 101, 83, 75, 74, 73, 59, 57, 45, 43, 41. Anal. Calcd for $C_{16}H_{32}O_3Si$ [300.51]: C, 63.95; H, 10.73. Found: C, 63.83; H, 10.68.

Syntheses of the independently synthesized reference compounds

(2*R)-Methoxy-(2*R**)-methyltetrahydrofuran (22a).** To a solution of 4,5-dihydro-2-methylfuran (7.00 g, 83.2 mmol) in dry MeOH (7 ml) were added 10 drops of acetic acid. After stirring for 15 min at 25°C and refluxing for 15 min the reaction mixture was cooled to 25°C and neutralized with five spatula tips of NaOMe. The suspension was filtered and the filtrate was distilled (113–115°C, 60 mm) giving the volatile acetal **22a** (3.84 g, 40%) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93–3.80 (m, 2H), 3.20 (s, 3H), 2.09–1.96 (m, 2H), 1.94–1.83 (m, 1H), 1.79–1.68 (m, 1H), 1.42 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 107.1, 67.1, 48.1, 37.6, 24.2, 20.8; IR (NaCl) 2987, 2948, 2884, 2827, 1460, 1378, 1323, 1243, 1201, 1156, 1119, 1069, 1028, 900, 845 cm^{-1}; MS (EI) *m/z* 117 (M+H$^+$) 101, 86, 85, 83, 75, 74, 73, 72, 71, 59, 57, 55, 53, 45, 44, 43, 42, 41. Anal. Calcd for $C_6H_{12}O_2$ [116.16]: C, 62.04; H, 10.41; O, 27.55. Found: C, 61.80; H, 10.31; O, 27.73.

(3*S)-Hydroxy-(2*R**)-methyltetrahydrofuran.** To a solution of 4,5-dihydro-2-methylfuran (10.0 g, 119 mmol) in dry THF (100 ml) was added at 0°C carefully borane–dimethyl sulfide complex (9.04 g, 119 mmol). After stirring for 1 h at 25°C the reaction mixture was cooled again to 0°C followed by a slow addition of 3 N NaOH solution (42 ml) and 30% H_2O_2 solution (20 ml). After completion of the addition the suspension was stirred for 6 h at 25°C followed by an addition of K_2CO_3 (65.0 g). Transferring the suspension in a separatory funnel the organic layer was separated. The aqueous phase was extracted with Et_2O (3×250 ml) and the organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (Uetikon, pentane/acetone 5/1→2/1) yielding the desired furanol (4.62 g, 38%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.99–3.89 (m, 3H), 3.82 (qd, J=6.4, 3.4 Hz, 1H), 3.59 (d, J=4.1 Hz, 1H), 2.15 (dtd, J=13.0, 8.6, 6.4 Hz, 1H), 1.85 (dddd, J=13.0, 6.7, 4.3, 3.2 Hz, 1H), 1.19 (d, J=6.4 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 81.8, 76.8, 66.0, 34.3, 18.8; IR (NaCl) 3418, 2972, 2932, 2877, 1707, 1446, 1377, 1314, 1252, 1188, 1089, 1008, 984, 942, 870, 833 cm^{-1}; MS (EI) *m/z* 102 (M$^+$), 87, 83, 71, 69, 59, 58, 57, 56, 55, 53, 45, 44, 43, 42, 41. Anal. Calcd for $C_5H_{10}O_2$ [102.13]: C, 58.80; H, 9.87; O, 31.33. Found: C, 58.57; H, 9.65; O, 31.32.

(2*S)-Methyl-(3*S**)-phenylcarbonyloxytetrahydrofuran.** To a solution of DEAD (6.82 g, 39.2 mmol) and benzoic acid (4.78 g, 39.2 mmol) in dry Et_2O (20 ml) was added a solution of P(Ph)$_3$ (10.6 g, 39.2 mmol) and (3*S**)-hydroxy-(2*R**)-methyltetrahydrofuran (2.00 g, 19.6 mmol) in dry Et_2O (30 ml) over a period of 5 min with intermediate cooling to guarantee 25°C. After stirring for 4 h the suspension was filtered, the residue washed with Et_2O and the filtrate concentrated in vacuo. The crude product was purified by chromatography (Uetikon, pentane/acetone 20/1→5/1) yielding the ester (2.77 g, 69%) as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09–7.99 (m, 2H), 7.60–7.52 (m, 1H), 7.47–7.39 (m, 2H), 5.51 (ddd, J=6.1, 3.9, 2.1 Hz, 1H), 4.11 (td, J=8.3, 6.8 Hz, 1H), 4.03 (qd, J=6.4, 2.9 Hz, 1H), 3.83 (td, J=8.6, 5.6 Hz, 1H), 2.42 (dddd, J=13.9, 8.7, 6.9, 6.1 Hz, 1H), 2.14 (dddd, J=13.8, 7.9, 5.8, 2.1 Hz, 1H), 1.32 (d, J=6.4 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.0, 133.0, 130.1, 129.6, 128.4, 77.6, 75.8, 66.0, 33.6, 14.4; IR (NaCl) 3063, 2983, 2938, 2871, 1718, 1602, 1584, 1491, 1451, 1384, 1356, 1314, 1275, 1176, 1156, 1114, 1089, 1070, 1026, 993, 948, 900, 859, 806, 713 cm^{-1}; MS (FAB, NBA) *m/z* 207, 206 (M$^+$), 205, 191, 149, 123, 106, 105, 101, 85, 84, 83, 77, 71, 69, 57, 55, 51, 50, 45, 43, 41, 39. Anal. Calcd for $C_{12}H_{14}O_3$ [206.24]: C, 69.88; H, 6.84; O, 23.27. Found: C, 69.73; H, 6.68; O, 23.40.

(3*S)-Hydroxy-(2*S**)-methyltetrahydrofuran.** A solution of (2*S**)-Methyl-(3*S**)-phenylcarbonyloxytetrahydrofuran (6.60 g, 32.0 mmol) and NaOMe (~1 g) in dry MeOH (70 ml) was stirred for 16 h. The reaction mixture was poured on sat. NaCl solution (150 ml) and the aqueous phase was extracted successively with Et_2O (5×150 ml), CH_2Cl_2 (3×150 ml) and ethyl acetate (3×150 ml). The organic layers were combined, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography (Uetikon, pentane/acetone 5/1) giving the furanol (2.20 g, 67%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.17 (s, 1H), 4.04 (q, J=7.9 Hz, 1H), 3.80–3.71 (m, 2H), 2.52 (s, 1H), 2.28–2.16 (m, 1H), 1.99–1.90 (m, 1H), 1.27 (d, J=6.4 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 78.5, 73.0, 65.5, 35.6, 13.8; IR (NaCl) 3416, 2976, 2935, 2876, 1440, 1382, 1354, 1331, 1291, 1196, 1155, 1128, 1082, 1021, 991, 972, 907, 868, 836, 734 cm^{-1}; MS (EI) *m/z* 102 (M$^+$), 87, 83, 71, 69, 59, 58, 57, 56, 55, 53, 45, 44, 43, 42, 41. Anal. Calcd for $C_5H_{10}O_2$ [102.13]: C, 58.80; H, 9.87; O, 31.33. Found: C, 58.33; H, 9.60; O, 31.79.

(3*S)-Methoxy-(2*R**)-methyltetrahydrofuran (21a1).** To a solution of KOH (5.17 g, 78.3 mmol) in dry DMSO (20 ml) was added slowly (3*S**)-hydroxy-(2*R**)-methyltetrahydrofuran (2.00 g, 19.6 mmol) followed by MeI (5.56 g, 39.2 mmol) using intermediately a cooling bath. After stirring for 30 min at 25°C the reaction mixture was poured on H_2O (150 ml) and the aqueous phase was extracted with CH_2Cl_2 (4×100 ml). The organic extracts were combined, washed with H_2O (5×200 ml), dried over $MgSO_4$ and concentrated carefully in vacuo. After distillation (116–118°C, 760 mm) the volatile **21a1** (1.05 g, 46%) was obtained as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (td, J=8.4, 3.5 Hz, 1H), 3.89 (qd, J=6.2,

3.5 Hz, 1H), 3.83 (td, *J*=8.8, 6.8 Hz, 1H), 3.53 (dt, *J*=6.3, 3.1 Hz, 1H), 3.33 (s, 3H), 2.05 (dddd, *J*=13.1, 9.2, 8.2, 6.5 Hz, 1H), 1.91 (ddt, *J*=13.1, 6.6, 3.3 Hz, 1H), 1.23 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 86.7, 79.4, 66.4, 56.8, 31.5, 19.5; IR (NaCl) 2973, 2932, 2876, 2825, 1708, 1641, 1456, 1373, 1207, 1118, 1067, 1020, 952, 854 cm^{-1}; MS (EI) *m/z* 116 (M^+), 115, 101, 85, 83, 73, 72, 71, 59, 58, 57, 55, 45, 43, 42, 41. Anal. Calcd for $C_6H_{12}O_2$ [116.16]: C, 62.04; H, 10.41; O, 27.55. Found: C, 61.80; H, 10.50; O, 27.26.

(3*S)-Methoxy-(2*S**)-methyltetrahydrofuran (21a2).** As in the preparation of **21a1**, KOH (5.17 g, 78.3 mmol) in dry DMSO (20 ml), adding (3*S**)-hydroxy-(2*S**)-methyltetrahydrofuran (2.00 g, 19.6 mmol) at 25°C, MeI (5.56 g, 39.2 mmol) at 0°C and stirring for 3 h at 25°C yielded the volatile **21a2** (596 mg, 26%) after work-up and distillation (110–112°C, 760 mm) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (dt, *J*=8.0, 7.6 Hz, 1H), 3.85 (qd, *J*=6.4, 4.2 Hz, 1H), 3.76–3.69 (m, 2H), 3.34 (s, 3H), 2.07–2.01 (m, 2H), 1.25 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 81.9, 77.8, 65.6, 57.0, 31.5, 14.1; IR (NaCl) 2976, 2934, 2880, 2829, 2696, 1641, 1452, 1381, 1353, 1293, 1209, 1154, 1090, 1047, 1019, 989, 942, 879, 850, 694 cm^{-1}; MS (EI) *m/z* 101, 85, 83, 73, 72, 71, 59, 58, 57, 55, 45, 43, 42, 41. Anal. Calcd for $C_6H_{12}O_2$ [116.16]: C, 62.04; H, 10.41; O, 27.55. Found: C, 61.84; H, 10.28; O, 27.63.

(3*S)-Cyano-(2*R**)-methyltetrahydrofuran (21b1) and (3*S**)-cyano-(2*S**)-methyltetrahydrofuran (21b2).** To a solution of (2*R**)-methyltetrahydrofuran-3-one (2.50 g, 25.0 mmol) and TosMIC (4.88 g, 25.0 mmol) in dimethoxyethane (20 ml) was added at 0°C a solution of KO^{t}Bu (5.78 g, 50.0 mmol) in ^{t}BuOH (50 ml) and dimethoxyethane (30 ml). After stirring for 45 min at 0°C and 1 h at 25°C the reaction mixture was poured on H_2O (300 ml) and the aqueous phase was extracted with Et_2O (4×200 ml). The combined organic layers were dried over $MgSO_4$ and concentrated carefully in vacuo. The diastereomers were separated and purified by chromatography (Uetikon, pentane/Et_2O 1/1) giving compound **21b1** (457 mg, 17%) and **21b2** (453 mg, 16%) as colorless oils: **21b1:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06–3.97 (m, 2H), 3.87 (td, *J*=8.5, 6.9 Hz, 1H), 2.56 (dt, *J*=9.4, 7.9 Hz, 1H), 2.37 (dddd, *J*=12.5, 9.5, 7.8, 6.8 Hz, 1H), 2.23 (dtd, *J*=12.8, 7.8, 5.2 Hz, 1H), 1.39 (d, *J*=6.1 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 119.9, 78.5, 67.0, 34.9, 30.8, 19.0; IR (NaCl) 2978, 2935, 2876, 2242, 1457, 1387, 1360, 1306, 1242, 1126, 1098, 1052, 1024, 940, 869 cm^{-1}; MS (EI) *m/z* 111 (M^+), 96, 82, 80, 70, 69, 68, 67, 66, 64, 58, 55, 54, 53, 52, 51, 45, 43, 42, 41. Anal. Calcd for C_6H_9NO [111.14]: C, 64.84; H, 8.16; N, 12.60; O, 14.40. Found: C, 64.78; H, 8.10; N, 12.52; O, 14.40. **21b2:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (td, *J*=8.3, 5.6 Hz, 1H), 4.02 (quint, *J*=6.2 Hz, 1H), 3.75 (ddd, *J*=8.9, 6.8, 6.8 Hz, 1H), 3.13 (ddd, *J*=8.4, 6.1, 4.8 Hz, 1H), 2.42–2.23 (m, 2H); 1.45 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 119.3, 75.2, 66.4, 34.0, 31.0, 17.4; IR (NaCl) 2982, 2938, 2881, 2241, 1455, 1388, 1357, 1293, 1241, 1183, 1149, 1122, 1081, 1056, 1024, 996, 938, 865, 691 cm^{-1}; MS (EI) *m/z* 111 (M^+), 96, 82, 80, 70, 69, 68, 67, 66, 64, 58, 55, 54, 53, 52, 45, 43, 42, 41. Anal. Calcd for C_6H_9NO [111.14]: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.75; H, 8.22; N, 12.60. The relative stereochemistry of **21b1** and **21b2** was determined by NOEDIF experiments.

(3*S)-*N*,*N*-Dimethylamino-(2*R**)-methyltetrahydrofuran (21c1) and (3*S**)-*N*,*N*-dimethylamino-(2*S**)-methyltetrahydrofuran (21c2).** To a stirred solution of (2*R**)-methyltetrahydrofuran-3-one (3.00 g, 30.0 mmol) in dry MeOH (200 ml) were added molecular sieve 4 Å (4.00 g) and $Me_2NH{\cdot}HCl$ (14.9 g, 180 mmol). This suspension was treated with a solution of $NaBH_3CN$ (1.32 g, 21.0 mmol) in MeOH (20 ml) over a period of 15 min and stirred for 30 h. After passing through Celite and concentration of the filtrate to a volume of ~100 ml in vacuo the remaining solution was poured on H_2O (100 ml) and the aqueous phase was extracted with Et_2O (5×150 ml). The organic extracts were combined, dried over $MgSO_4$ and concentrated carefully in vacuo. The diastereomers were separated and purified by chromatography (Merck, MeOH) giving, after each fraction was de novum dissolved in Et_2O (10 ml), filtered and concentrated in vacuo, compound **21c1** (388 mg, 10%), compound **21c2** (1.13 g, 29%) and a 3/1 mixture of **21c1/21c2** (527 mg, 14%) as colorless oils: **21c1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (quint, *J*=5.9 Hz, 1H), 3.88–3.77 (m, 2H), 2.54 (dt, *J*=8.0, 5.7 Hz, 1H), 2.26 (s, 6H), 2.03–1.88 (m, 2H), 1.27 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 77.1, 72.6, 66.4, 43.2, 29.0, 20.4; IR (NaCl) 2971, 2868, 2824, 2778, 2242, 1658, 1460, 1376, 1263, 1159, 1100, 1071, 1042, 901, 857, 733 cm^{-1}; MS (EI) *m/z* 130, 129 (M^+), 100, 86, 85, 84, 71, 70, 68, 58, 57, 56, 44, 43, 42, 41. Anal. Calcd for $C_7H_{15}NO$ [129.20]: C, 65.07; H, 11.70; N, 10.84; O, 12.38. Found: C, 64.78; H, 11.46; N, 10.85; O, 12.75. **21c1:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (quint, *J*=6.3 Hz, 1H), 3.99 (td, *J*=8.7, 3.9 Hz, 1H), 3.81 (q, *J*=8.4 Hz, 1H), 2.67 (ddd, *J*=9.3, 7.4, 6.1 Hz, 1H), 2.24 (s, 6H), 2.03–1.85 (m, 2H), 1.14 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 76.2, 68.9, 65.6, 45.0, 28.1, 15.0; IR (neat) 2976, 2871, 2819, 2775, 2598, 1657, 1458, 1379, 1347, 1278, 1208, 1160, 1120, 1084, 1066, 1033, 942, 894, 859 cm^{-1}; MS (EI) *m/z* 130, 129 (M^+), 100, 86, 85, 84, 71, 70, 68, 58, 57, 56, 44, 43, 42, 41. Anal. Calcd for $C_7H_{15}NO$ [129.20]: C, 65.07; H, 11.70; N, 10.84. Found: C, 64.74; H, 11.53; N, 10.81. The relative stereochemistry of **21c1** and **21c2** was determined by *cis*-γ-effects.

Acknowledgements

We would like to thank Prof. William. L. Jorgensen and his coworkers Dr Daniel L. Severance and Dr Nora McDonald from the Yale University, New Haven, and Prof. Sason Shaik from the Hebrew University, Jerusalem, for their scientific support. We are grateful to the Swiss National Science Foundation for financial support. Hendrik Zipse and Matthias Mohr thank the Volkswagen Stiftung and the Fonds der Chemischen Industrie for financial support.

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