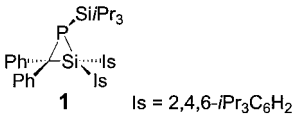
A Novel CSiP Ring from the Reaction of a Complexed Phosphinidene and a Silene**

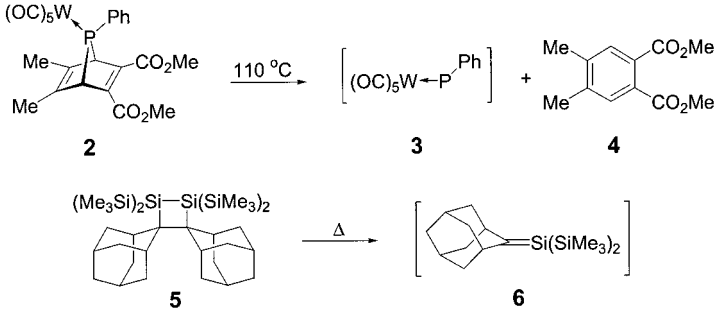
Mark J. M. Vlaar, Andreas W. Ehlers, Frans J. J. de Kanter, Marius Schakel, Anthony L. Spek, Martin Lutz, Nadejda Sigal, Yitzhak Apeloig, and Koop Lammertsma*

Cyclopropanes and their three-membered heterocyclic analogues have long-been recognized as important chemical structures. Even three-membered rings containing the second-row elements phosphorus and silicon are now well established. Moreover, many phosphiranes and siliranes are already known containing a second heteroatom such as O,[1] N,[2] or S.[3] However, no phosphasilirane has yet been isolated. So far, only ^{31}P and ^{29}Si NMR data have been reported by Drieß and Pritzkow for a CPSi ring structure (**1**), which they could not isolate from the reaction mixture.[4] Here we report on a novel synthesis leading to a transition metal complexed phosphasilirane, and present its spectroscopic characterization and single-crystal structure determination as well as the results of G3(MP2) ab initio calculations on the strain energy of the parent $CPSiH_5$ compound.



1 Is = 2,4,6-*i*Pr$_3$C$_6$H$_2$

In situ generated terminal complexed phosphinidenes such as **3**[5] are convenient singlet carbene-like building blocks[6] for the synthesis of phosphirane complexes by addition to olefins.

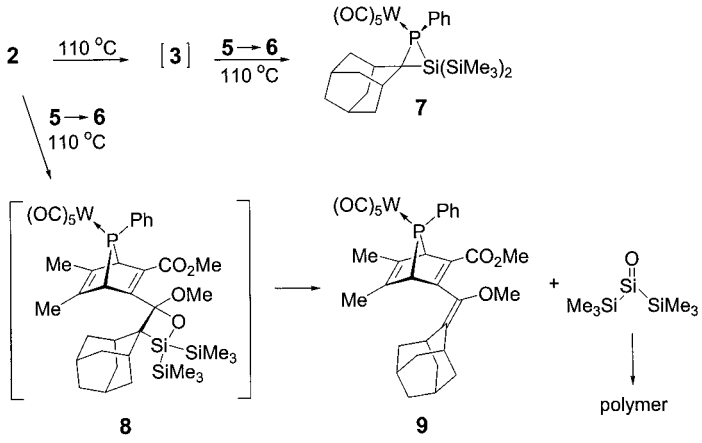


2 **3** **4**

5 **6**

Hence, the addition of this phosphinidene to a silene seemed to us an obvious path to a phosphasilirane complex. However, only a few stable silenes have been synthesized and the number of methods that give transient silenes under the reaction conditions used to generate **3** is even more limited.[7] A welcome exception is silene **6**,[8] which is generated in situ by retrocycloaddition from its dimer **5.** Silene **6** has been applied successfully as a building block in several high-yield trapping reactions.[8, 9] The thermal equilibrium between the silene and its dimer is most effective at around 100 °C, the temperature at which complexed phosphinidene **3** is generated. Therefore **6** appeared to us as a plausible candidate to explore the reactivity of silenes toward complexed phosphinidenes.

To maximize the concentration of the two reactive intermediates (phosphinidene complex **3** and silene **6**), a mixture of silene dimer **5** and a twofold excess (based on silene) of phosphinidene precursor **2** was heated in toluene at 110 °C. After 90 min the reaction was stopped, and the reaction mixture was purified by column chromatography at −15 °C to give after crystallization bright yellow crystals of phosphasilirane complex **7** and light yellow crystals of **9** in remarkably high yields of 25 and 30 %, respectively.



7 **8** **9**

Phosphasilirane **7** is a remarkably stable compound with characteristic spectroscopic properties. Compared to the data for the reported phosphasilirane **1**, its ^{31}P NMR resonance at $\delta = -116.9$ is deshielded by 80.5 ppm, its ^{29}Si NMR resonance at $\delta = -97.9$ is shielded by 43.4 ppm, and its $^{(1+2)}J(P,Si)$ coupling constant of 22.9 Hz is smaller by 26.8 Hz. These differences between **7** and **1** may be attributed to the presence of the $W(CO)_5$ and $Si(CH_3)_3$ substituents. The $^1J(P,W)$ coupling constant of 213.6 Hz for **7** is about 40 Hz smaller than is generally observed for $W(CO)_5$-complexed 1-phenylphosphiranes. This is consistent with its rather long P–W bond of 2.5509(9) Å (Figure 1).[10] Likewise, the P1–C1 bond of **7** of 1.880(3) Å is slightly elongated and its endocyclic angle at P1 of 54.60(11)° is accordingly larger by 5°.[11] The Si1–C1 bond length of 1.919(3) Å and the endocyclic bond angle at Si1 of 52.99(10)° are slightly larger than those typically observed in siliranes.[12]

Silene **5** does not only react with the in situ generated phosphinidene complex **3** but also with its precursor **2** to give **9**. The ^{31}P NMR resonance of **9** at $\delta = 184.4$ is characteristic for a 7-phosphanorbornadiene. Due to the absence of ^{29}Si NMR chemical shifts and the complexity of both the ^1H and

[*] Prof. Dr. K. Lammertsma, M. J. M. Vlaar, Dr. A. W. Ehlers, Dr. F. J. J. de Kanter, Dr. M. Schakel
Department of Organic and Inorganic Chemistry
Faculty of Sciences, Vrije Universiteit
De Boelelaan 1083, 1081 HV, Amsterdam (The Netherlands)
Fax: (+31) 20-444-7488
E-mail: lammert@chem.vu.nl
Dr. A. L. Spek, Dr. M. Lutz
Bijvoet Center for Biomolecular Research
Crystal and Structural Chemistry, Utrecht University
Padualaan 8, 3584 CH, Utrecht (The Netherlands)
N. Sigal, Prof. Dr. Y. Apeloig
Department of Chemistry
Technion-Israel Institute of Technology, Haifa 32000 (Israel)

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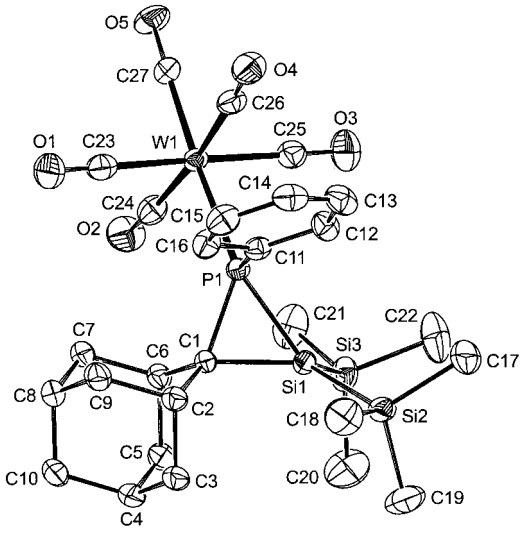


Figure 1. Structure of **7** in the crystal (displacement ellipsoids drawn at the 50% probability level; hydrogen atoms are omitted for clarity). Selected bond lengths [Å], angles, and torsion angles [°]: P1-W1 2.5510(9), P1-Si1 2.2436(13), P1-C1 1.880(3), Si1-C1 1.918(3), Si1-Si2 2.3699(14), Si1-Si3 2.3603(15), C1-C2 1.541(5), C1-C6 1.536(5); Si1-P1-C1 54.59(11), P1-Si1-C1 53.00(10), Si1-C1-P1 72.41(12), W1-P1-C11 110.17(11), C2-C1-C6 109.3(3), Si2-Si1-Si3 114.12(6); W1-P1-Si1-C1 −111.73(14), C11-P1-C1-Si1 −94.76(15).

^{13}C NMR spectra, we resorted to a single-crystal X-ray structure determination (Figure 2)[10] to establish the structure of **9**. Its formation is readily rationalized by a [2+2] cycloaddition of the silene to an ester carbonyl group of **2**, giving the rather crowded compound **8**, which undergoes a [2+2] retroaddition to afford **9** and a silanone. The latter is not observed as it polymerizes instantaneously. While we did not observe intermediate **8** there is ample precedence for the formation of 1,2-silaoxetanes from silenes and non-enolizable ketones as well as for its dissociation into alkenes and silanones.[13] It is relevant to note in this context that the [2+2] cycloaddition of an ester and a silene is also a first; silene additions to α,β-unsatured esters have been reported to occur in a [4+2] fashion.[14] The formation of **9** is all the more remarkable, since 7-phosphanorbornadiene complexes usually decompose quite rapidly at 110 °C (e.g. **2** → **3**) and the same would be expected for **9**. Because the crystal structures of **9** and the $Cr(CO)_5$ complex of **2**[15] show very similar bond lengths and angles for the 7-phosphanorbornadiene unit, we speculate that the higher thermal stability of **9** toward cheletropic elimination of $PhPW(CO)_5$ is related to a reduced exothermicity for formation of the aromatic fragment.

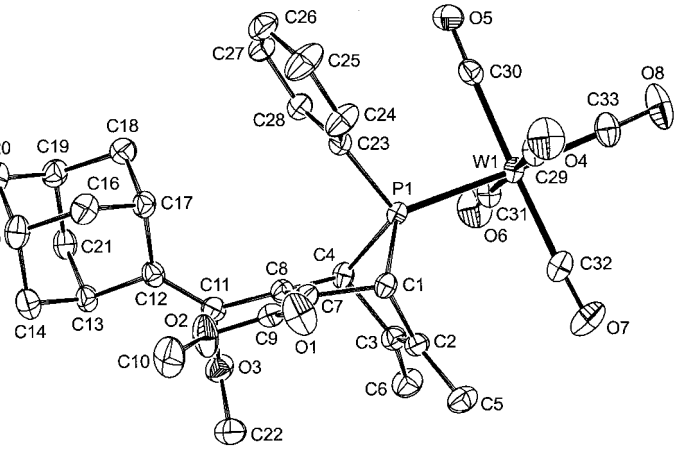
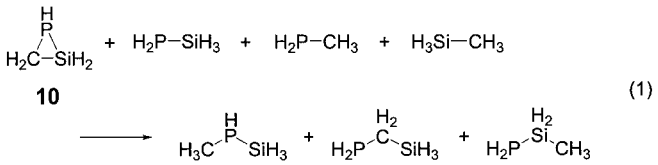


Figure 2. Structure of **9** in the crystal (displacement ellipsoids drawn at the 50% probability level; hydrogen atoms are omitted for clarity). Selected bond lengths [Å], and angles [°]: P1-W1 2.4846(6), P1-C1 1.866(2), P1-C4 1.876(2), P1-C23 1.823(2), C1-C2 1.546(3), C3-C4 1.541(3), C2-C3 1.336(3), C1-C7 1.523(3), C4-C8 1.529(3), C7-C8 1.356(3), C8-C11 1.479(3), C11-C12 1.334(3); C1-P1-C4 79.29(10), P1-C1-C2 97.00(15), P1-C4-C3 96.41(14), C1-P1-W1 123.15(8), C4-P1-W1 123.76(7), P1-C1-C7 101.72(15), P1-C4-C8 102.40(15).

We resorted to ab initio MO theory to obtain the strain energy for the parent phosphasilirane **10**, the MP2 geometry of which is given in Figure 3. Comparison with the X-ray crystal structure of **7** shows that the bond lengths within the CPSi ring of **7** are 0.02 Å (Si–P), 0.03 Å (C–P), and 0.06 Å (C–Si) longer than in the parent **10**, reflecting the effect of steric congestion around the ring. From the ΔH_f values calculated at G3(MP2)[16] for **10** (30.5 kcal mol^{-1}) and the other molecules of the homodesmotic reaction shown in Equation (1), a strain



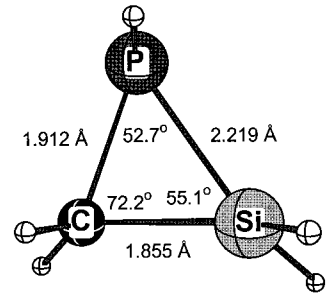


Figure 3. MP2-optimized structure of phosphasilirane $PSiH_5$.

energy of 26.5 kcal mol^{-1} is deduced. This strain energy is similar in magnitude to that of cyclopropane and larger than that of phosphirane (22.2 kcal mol^{-1}),[17] but substantially smaller than the value of 42.3 kcal mol^{-1} for silirane (all G3(MP2)).[18] This reduction in strain energy of 16.9 kcal mol^{-1} from the large value for silirane has been related to the preference of Si for angles near 90°.[18a] The elongated bond lengths of phosphasilirane ($CPSiH_5$) as compared to silirane (C_2SiH_6) enlarge the endocyclic angle at Si from 49.0 to 52.7.

Experimental Section

The experiment was performed under an atmosphere of dry nitrogen. NMR spectra were recorded on Bruker WM 250 (^{31}P) and MSL 400 (^1H, ^{13}C, ^{29}Si) spectrometers by using $SiMe_4$ (^1H, ^{13}C, ^{29}Si) and 85% H_3PO_4 (^{31}P) as external standards. High-resolution mass spectra (HRMS) were recorded on a Jeol HX-1010 and IR spectra on a Mattson 630 Galaxy spectrophotometer.

7 and **9**: Silene dimer **5** (0.17 g, 0.28 mmol) and complex **2** (0.73 g, 1.1 mmol) were heated in refluxing toluene (10 mL) for 90 min. Workup by solvent evaporation, chromatography (−15 °C, activated silica (pentane/CH_2Cl_2 (3/1); CH_2Cl_2)), and crystallization (hexane/CH_2Cl_2) yielded yellow crystals of **7** (0.10 g, 25%, bright) and **9** (0.12 g, 30%, pale).

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7: m.p. 159–161 °C; ^{29}Si NMR (C_6D_6): $\delta = -9.0$ (d, ^2J(Si,P) = 4.7 Hz; $Si(CH_3)_3$), −10.3 (d, ^2J(Si,P) = 4.1 Hz; $Si(CH_3)_3$), −97.9 (d, $^{(1+2)}J$(Si,P) = 22.9 Hz; PSi); ^{31}P NMR (C_6D_6): $\delta = -116.9$ (^1J(P,W) = 213.6 Hz); ^{13}C NMR (C_6D_6): δ = 199.6 (d, ^2J(C,P) = 25.5 Hz; *trans*-CO), 198.5 (d, ^2J(C,P) = 6.8 Hz, ^1J(C,W) = 126.4 Hz; *cis*-CO), 138.8 (d, ^1J(C,P) = 15.2 Hz; *ipso*-Ph), 129.4 (d, ^4J(C,P) = 1.9 Hz; *p*-Ph), 128.8 (d, ^2J(C,P) = 8.6 Hz; *o*-Ph), 128.5 (*m*-Ph), 43.7 (d, ^1J(C,P) = 34.6 Hz; P*C*Si), 41.9 (d, J(C,P) = 6.4 Hz; adamantyl(Ad)-CH_2), 41.3 (d, J(C,P) = 13.8 Hz; Ad-CH_2), 38.8 (s; Ad-CH_2), 38.4 (s; Ad-CH_2), 36.8 (d, J(C,P) = 4.1 Hz; Ad-CH), 36.3 (d, J(C,P) = 2.4 Hz; Ad-CH_2), 33.7 (d, J(C,P) = 6.2 Hz; Ad-CH), 28.6 (s; Ad-CH), 28.1 (s; Ad-CH), 2.3 (d, ^3J(C,P) = 1.6 Hz; CH_3), 1.7 (s; CH_3); ^{1}H NMR (C_6D_6): δ = 7.6–7.7 (m, 2H; Ph), 7.0–7.1 (m, 3H; Ph), 1.8–2.9 (m, 14H; Ad), 0.48 (s, 9H, CH_3), 0.00 (s, 9H, CH_3); HRMS: calcd. for $C_{27}H_{37}Si_3PO_5W$: 740.11963; found: 740.1212; IR (CH_2Cl_2): $\tilde{\nu}$ = 1933 (s), 2066 (w) (ν(CO)) cm^{-1}.

9: m.p. 167–168 °C; ^{31}P NMR ($CDCl_3$): δ = 184.4 (^1J(P,W) = 235.1 Hz); ^{13}C NMR ($CDCl_3$): δ = 199.4 (d, ^2J(C,P) = 25.0 Hz; *trans*-CO), 196.7 (d, ^2J(C,P) = 6.7 Hz, ^1J(C,W) = 125.4 Hz; *cis*-CO), 165.5 (d, ^3J(C,P) = 3.0 Hz; C=O), 153.7 (d, ^3J(C,P) = 4.9 Hz; O−*C*=C), 142.5 (d, ^2J(C,P) = 12.5 Hz; C=*C*−C=O), 139.3 (d, ^1J(C,P) = 17.6 Hz; *ipso*-Ph), 138.7 (d, ^2J(C,P) = 11.6 Hz; C=*C*CH_3), 138.5 (s; *C*=C-CH_3), 136.8 (d, ^2J(C,P) = 2.7 Hz; *C*=C−C=O), 136.3 (s; O−C=*C*), 128.8–129.6 (m; Ph), 64.3 (d, ^1J(C,P) = 19.0 Hz; PCH), 58.7 (s; C=C−O*C*H_3), 57.0 (d, ^1J(C,P) = 23.1 Hz; PCH), 51.9 (s, O=C-O-*C*H_3), 39.3 (s, Ad-CH_2), 39.2 (s, Ad-CH_2), 38.6 (s, Ad-CH_2), 37.3 (s, Ad-CH_2), 32.7 (s, Ad-CH), 30.3 (s, Ad-CH), 28.6 (s, Ad-CH), 28.5 (s, Ad-CH), 16.4 (d, ^3J(C,P) = 2.2 Hz; CH_3), 16.2 (d, ^3J(C,P) = 2.1 Hz; CH_3); ^{1}H NMR ($CDCl_3$): δ = 7.2–7.4 (m, 5H; Ph), 4.2 (d, 1H, ^4J(H,H) ≈ 3.0 Hz; PCH), 3.7 (pseudo-t, 1H, ^4J(H,H) ≈ ^2J(H,P) ≈ 3.0 Hz; PCH), 3.7 (s, 3H; H_3CO−C=O), 3.0 (m, 1H; CH-Ad), 2.8 (s, 3H; H_3C-O-C=O), 2.1 (s, 3H; C=C-CH_3), 2.0 (s, 3H; C=C-CH_3), 1.3–1.9 (m, 13H; Ad); HRMS: calcd for $C_{27}H_{37}Si_3PO_5W$ (%): 772.14227; found: 772.1379; IR (CH_2Cl_2): $\tilde{\nu}$ = 1939 (s), 2070 (w) (ν(CO)) cm^{-1}.

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[10] Crystal structure determinations: Intensities were measured on a Nonius KappaCCD diffractometer with rotating anode and graphite monochromator ($Mo_{K\alpha}$, λ = 0.71073 Å) at a temperature of 150(2) K up to a resolution of $(\sin\theta/\lambda)_{max}$ = 0.65 Å^{-1}. The absorption correction was based on multiple symmetry-related measurements (program PLATON,[19] routine MULABS). The structures were solved with Patterson methods (program DIRDIF97)[20] and refined with the program SHELXL97[21] against F^2 of all reflections. Non-hydrogen atoms were refined freely with anisotropic displacement parameters. Hydrogen atoms were located in the difference Fourier map and refined as rigid groups in **7** and freely with isotropic parameters in **9**. The drawings, structure calculations, and checking for higher symmetry were performed with the program PLATON. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-143305 (**7**) and CCDC-143306 (**9**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). **7**: $C_{27}H_{37}O_5PSi_3W$, M_r = 740.66, yellow block, 0.45 × 0.45 × 0.27 mm^3, monoclinic, $P2_1/c$, a = 15.3659(3), b = 11.4824(2), c = 18.1428(4) Å, β = 93.0095(10)°, V = 3196.65(11) Å^3, Z = 4, ρ = 1.539 g cm^{-3}, 59674 measured reflections, 7308 unique reflections (R_{int} = 0.068). Absorption correction: μ = 3.808 mm^{-1}, 0.20–0.35 transmission. 340 refined parameters, no restraints. R ($I > 2\sigma(I)$): $R1$ = 0.0293, $wR2$ = 0.0721. R (all data): $R1$ = 0.0315, $wR2$ = 0.0729; S = 1.215; max./min. residual electron density = −1.74/1.53 e Å^3. **9**: $C_{33}H_{33}O_8PW$, M_r = 772.41, yellow block, 0.45 × 0.24 × 0.24 mm^3, triclinic, $P\bar{1}$, a = 11.2268(2), b = 11.9268(2), c = 12.8261(2) Å, α = 70.3309(7), β = 74.1527(7), γ = 82.6207(7)°, V = 1554.48(5) Å^3, Z = 2, ρ = 1.650 g cm^{-3}, 28950 measured reflections, 7118 unique reflections (R_{int} = 0.051). Absorption correction: μ = 3.817 mm^{-1}, 0.26–0.41 transmission. 520 refined parameters, no restraints. R ($I > 2\sigma(I)$): $R1$ = 0.0216, $wR2$ = 0.0522. R (all data): $R1$ = 0.0232, $wR2$ = 0.0529. S = 1.071; min./max. residual electron density = −0.97/1.50 e Å^3.

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Virtual Screening for Bioactive Molecules by Evolutionary De Novo Design**

Gisbert Schneider,* Odile Clément-Chomienne, Laurence Hilfiger, Petra Schneider, Stefan Kirsch, Hans-Joachim Böhm, and Werner Neidhart

One of the goals of computational chemistry is to be able to design novel molecular structures with biological activity comparable to a defined known drug (the "template") and with a significantly different architecture. There is a need to develop techniques that can be applied if a high-resolution receptor model is unavailable, complementing more conventional structure-based molecular modeling and design. Such algorithms would be particularly helpful for combinatorial library shaping and fast-follower strategies in drug development. Two major problems must be solved to successfully address this task. First, the tool must be able to systematically navigate and efficiently search in a vast chemical space containing billions of virtual compounds, as it is impossible to exhaustively screen all possible molecules for a desired biological activity. Second, the conceptual view of a molecule must be defined in such a way that allows rapid comparison of the template with novel compounds, yielding a measure of functional rather than structural similarity.

For the sake of "backbone (scaffold)-switching" the various pharmacophore concepts provide a straightforward approach.[1] Adaptive stochastic searching, notably evolutionary algorithms, represents a practicable solution to optimization in a high-dimensional search space. This is especially true when no or only little information is available about the ruggedness of the associated "fitness landscape".[2] Here we present an efficient computational molecular design strategy that implements pharmacophore-guided evolutionary searching in chemical space. Experimental proof of the concepts is demonstrated by the successful de novo design of a new structural class of potent K^+-channel inhibitors. The algorithm is referred to as TOPAS (*TOP*ology-*A*ssigning *S*ystem) in this report.[3] TOPAS provides a solution to template-based de novo design, in which novel molecules are assembled taking a given bioactive compound as the reference point (template structure).

A challenging task in de novo design is the generation of molecular structures with "druglike" properties. To reduce the risk of generating molecular architectures with inadequate features, or which are difficult to synthesize—a problem encountered by many de novo design procedures[4]—TOPAS was equipped with a stock of building blocks obtained from retrosynthetic fragmentation of compounds listed in the Derwent World Drug Index (WDI).[5] The idea is that assembly of such building blocks by a limited set of chemical reactions might lead to chemically feasible novel structures, from both the medicinal chemistry and the synthesis planning perspective. All structures contained in the WDI, which had an entry related to "mechanism" or "activity", were subjected to retrosynthetic fragmentation. This approach is similar to the RECAP procedure developed by Hann and co-workers.[6] Eleven reaction schemes were applied to perform fragmentation (for details, see the original publication).[6] We used the Daylight tool kit for implementation of reaction schemes.[7] A total of 24563 unique building blocks was obtained from our analysis.[3] The same eleven reactions were used by TOPAS to assemble novel molecules.

TOPAS is based on a special evolutionary algorithm, a $(1,\lambda)$ evolution strategy.[2, 8] This type of evolutionary algorithm has been successfully applied to peptide design experiments in previous applications.[9] The common feature of evolutionary algorithms is a cyclic variation-selection process. "Parents" breed "offspring", and the fittest of each "generation" becomes the parent of the subsequent optimization cycle. Starting from an arbitrary point in search space (a randomly selected chemical structure), TOPAS generates a set of λ variant structures which satisfy a bell-shaped distribution centered in the chemical space coordinates of the parent structure. This means that most of the variants will be very similar to their parent, and the number of offspring at a certain distance point will be less as the distance-to-parent increases.[3] Distance in chemical space is defined by a topological pharmacophore measure (see below).

Evolution strategies are often applied to real-valued function optimization problems.[2] Algorithms generally operate directly on the parameters to be optimized, in contrast to genetic algorithms, which usually operate on a separately coded transformation of the objective variables (the so-called "chromosome").[10] In addition, evolution strategies include a second-level optimization of "strategy parameters", that is, tunable variables that in part determine how each parent will generate offspring. This enables an adaptive stochastic search to be performed and guarantees a finite probability of breeding very dissimilar structures ("snoopers" in chemical space).[9] The width of the variant distribution is determined by the variance or standard deviation, σ, of the bell-shaped curve reflecting the distance-to-parent probability. The σ

[*] Priv.-Doz. Dr. G. Schneider, O. Clément-Chomienne, L. Hilfiger, P. Schneider, S. Kirsch, H.-J. Böhm, W. Neidhart
Hoffmann-La Roche Ltd.
Pharmaceuticals Division
4070 Basel (Switzerland)
Fax: (+41) 61-68-8904
E-mail: gisbert.schneider@Roche.com

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