Case study #1: Strychnine

LD$_{50}$ = 0.16 mg/kg (rats)
Protecting-group-free synthesis as an opportunity for invention

Ian S. Young¹ and Phil S. Baran¹*

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Synthesis of Biotin - ~without- Protecting Groups

```
1. Na₂SO₃, H₂O
2. Li⁰, EtNH₂, LiNH₂
   ▶ C

1. mCPBA
2. H₂O
3. NaIO₄
   ▶ D

NaBH₄, MeOH
   ▶ E

Funk analysis:
2 rings
3 stereogenic centers
1 S atom
1 urea
7 points = 14 steps

MsCl, py.
   ▶ G

MsO
HN
NH
HN

1. Na₂S
2. NaOH
   ▶ H

biotin

```
The most efficient synthesis, the "ideal synthesis," has been defined by Hendrickson: "The ideal synthesis creates a complex skeleton ... in a sequence only of successive construction reactions involving no intermediary refunctionalizations, and leading directly to the structure of the target, not only its skeleton but also its correctly placed functionality."

Figure 1. A schematic view of redox economy in a synthetic sequence inspired by Evans’ lectures on the topic.[7]
In your presentations, identify **redox steps** and **protecting group steps** by color-coding. In the final analysis of each synthesis, summarize the total number of redox changes and the total number of protecting group steps (protecting installation = 1 step; protecting cleavage = 1 step). Identify protecting groups on the molecule structure of every intermediate in red; eg:

```
EtS
```

```
1. 1 N HCl, MeOH 55 °C
2. Ac₂O, py.
3. NaOMe, MeOH
4. TIPSCI, DMF, im.
51% 4 steps
```

```
(-)-diaboline
```

```
1. NaOMe, MeOH
2. NaOAc, Ac₂O
42%
```

```
5.2 mg
```

```
(-)-strychnine
```

Convergent Synthesis:

"Longest linear sequence" = 6 steps
Actual total steps = 9 steps

Linear Synthesis:
Funk Analysis

strychnine

7 rings
1 basic N
1 seven-membered ring
[1 alkene]
1 quaternary center
6 stereogenic centers

17 points = 34 steps maximum
Background:

Strychnine is a poisonous alkaloid isolated from the seeds of *Strychnos nux-vomica*, a small climbing shrub found in Africa, Asia and South America. Strychnine is still in use today as a rodent poison and was one of the first alkaloids isolated in a pure state (1818). The complete chemical structure of strychnine was not elucidated until 1947 by Woodward, Prelog and Robinson. In 1951, the X-ray crystal structure determination confirmed the proposed structure and the complete chemical synthesis was achieved by Prof. Robert B. Woodward of Harvard University in 1954. Below, is an excerpt of the introduction to a paper (*Tetrahedron*, 1963, 19, 247) by Woodward on the chemical synthesis which gives some interesting insight into the importance of strychnine and the state of alkaloid research after the second World War.
Strychnos nux vomica

seeds: 1.5% strychnine
Biosynthesis of Strychnine

Tryptamine + Secologanin → Strictosidine

Strictosidine + Glucose → Geissoschizine

Wieland-Gumlich aldehyde (open form) → Norfluorocurarine → Dehydropreakuammicine

Prestrychnine → Strychnine
THE TOTAL SYNTHESIS OF STRYCHNINE


Converse Memorial Laboratory, Harvard University, Cambridge, Massachusetts

(Received 30 October 1962)

STRYCHNINE The fearsome poisonous properties of this notorious substance attracted the attention of XVIIth century Europe to the Strychnos species which grow in the rain forests of the Southeast Asian Archipelagos and the Coromandel Coast of India, and gained for the seeds and bark of those plants a widespread use for the extermination of rodents, and other undesirables, as well as a certain vogue in medical practice — now known to be largely unjustified by any utility. The isolation of the pure alkaloid from the beans of Strychnos ignatii in 1818 by Pelletier and Caventou was an event of some historical importance, in that it provided a convincing and elegant demonstration of the correctness of the then only recently proposed and revolutionary suggestion that acid-fixing substances are produced in the vegetable kingdom.† Thus did circumstance early place ready at the hand of any interested chemist an abundant supply of a pure crystalline compound whose constitution and construction could hardly fail to excite curiosity. But organic chemistry, in its first hundred years, was scarcely equipped for the attack on so formidable an objective, and apart from the determination of the correct empirical formula of the alkaloid, and the discovery of a few simple transformations, no substantial progress was made until the commencement of the massive investigations of the present century. Then, over a period of forty years, one of the great classics of structural organic chemistry was constructed. In that effort, described in more than two hundred and fifty separate communications, Robert Robinson played a brilliant and commanding role, and the extensive beautiful experimental contributions of Hermann Leuchs were of definitive importance. In 1947, the task was finished,‡

* A preliminary communication and a general account describing this investigation have been published earlier.

† Pelletier and Caventou attributed this pioneer idea to Vauquelin, and in spite of that investigator's modest demurrer, wished to signalize his contribution by naming their new substance vauqueline. They were thwarted in their generous design by the officers of the Académie des Sciences at Paris, who delivered themselves of the opinion "qu'un nom chère ne pouvait être appliqué à un principe malfaisant"

‡ D. B. Robertson, Chem. Soc. 21 (1833), 127.
"Strychnine! The fearsome poisonous properties of this notorious substance attracted the attention of XVIth century Europe to the *Strychnos* species which grow in the rain forests of the Southeast Asian Archipelagos and the Coromandel Coast of India, and gained for the seeds and bark of those plants a widespread use for the extermination of rodents, and other undesirables, as well as a certain vogue in medical practice—now known to be largely unjustified by any utility. The isolation of the pure alkaloid from the beans of *Strychnos ignatii* in 1818 by Pelletier and Caventou was an event of some historical importance, in that it provided a convincing and elegant demonstration of the correctness of the then only recently proposed and revolutionary suggestion that acid-fixing substances are produced in the vegetable kingdom. Thus did circumstance early place ready at the hand of any interested chemist an abundant supply of a pure crystalline compound whose constitution and construction could hardly fail to excite curiosity. But organic chemistry, in its first hundred years, was scarcely equipped for the attack on so formidable an objective, and apart from the determination of the correct empirical formula of the alkaloid, and the discovery of a few simple transformations, no substantial progress was made until the commencement of the massive investigations of the present century. Then, over a period of forty years, one of the great classics of structural organic chemistry was constructed. In that effort, described in more than two hundred fifty separate communications, Robert Robinson played a brilliant and commanding role, and the extensive beautiful experimental contributions of Herman Leuchs were of definitive importance. In 1947, the task was finished and strychnine stood revealed as 1...It is now possible to contemplate the synthesis of the substance of which it has been said: "For its molecular size, it is the most complex substance known".."
Sir Robert Robinson & Robert Burns Woodward
Tetrahedron Publications
A footnote in this paper goes on:..."It will not be lost upon the reader-nor was it on at least some of the observers of the chemical scene in the late nineteen forties- that the almost simultaneous outcomes of decades-long chemical degradative assault, and the incomparably shorter X-ray crystallographic investigations, presaged a future in which so singular an edifice as the chemical structure determination of strychnine was unlikely to find parallels. But it is worthwhile to point out here that the establishment of the structure of strychnine was accompanied by no surcease of interesting chemical developments. The elucidation and further development of the fascinating chemistry of vomicine, the dramatic establishment of the relationships between strychnine and the calabash curare alkaloids, the discovery of intricate new transformations of the strychnine skeleton, the even now rapidly unfolding exciting new chapters in the story of the biogenesis of the Strychnos and related alkaloids, and perhaps also the synthesis here recorded, may be selected as only a few high points in the continuing evolution of the chemistry of strychnine during the last fifteen years. This short history should give pause to those whose talent for despair is lavished upon an organic chemistry ornamented and supplemented- or as they fancy, burdened- by magnificent new tools which permit the establishment in days or weeks of enlightenments which once would have required months or years. While it is undeniable that organic chemistry will be deprived of one special and highly satisfying kind of opportunity for the exercise of intellectual élan and experimental skill when the tradition of purely chemical structure elucidation declines, it is true too that the not infrequent dross of such investigation will also be shed; nor is there any reason to suppose that the challenge for the hand and the intellect must be less, or the fruits less tantalizing, when chemistry begins at the advanced vantage point of an established structure. Of course, men make much use of excuses for activities which lead to discovery, and the lure of unknown structures has in the past yielded a huge dividend of unsought fact, which has been of major importance of building organic chemistry as a science. Should a surrogate now be needed, we do not hesitate to advocate the case for synthesis."
Curare: alkaloid arrow poison extracts
Central and South America

Strychnos toxifera

Calabash gourd
Thirteen new total syntheses of strychnine have appeared since the classical Woodward synthesis. It is quite instructive to compare and contrast a few of these syntheses. The new syntheses have been reviewed by Beifuss wherein it is stated:

“Whether the four new total syntheses (to 1994) represent a fundamental improvement over Woodward’s strychnine synthesis and the extent of this improvement can certainly be debated. However, it can not be contested that Overman et al. accomplished the first enantioselective synthesis of the natural product, and that Kuehne and Rawal with their respective 17- and 15-step syntheses devised approaches with markedly fewer reaction steps than Woodward’s 28-, Magnus’ 27- and Overman’s 25-step syntheses.”
Woodward synthesis:

1. CH₂O, Me₂NH
   2. CH₃I

1. NaCN, DMF
   2. LiAlH₄

1. H₂CO₂Et
   2. TsCl, pyridine

1. NaBH₄
   2. Ac₂O, pyridine

1. LiAlH₄
   2. HBr, HOAc, Δ
   3. H₂SO₄

1. HCl, H₂O
   2. SeO₂

1. HC≡CNa, THF
   2. H₂, Lindlar’s cat.

STRYCHNINE
**Woodward Strychnine synthesis 1**

1. $\text{H}_2\text{C}=\text{O}, \text{Me}_2\text{NH}$
   $\text{HOAc, diox., H}_2\text{O}$
2. MeI

**mechanism: step 1**

**mechanism: step 1**
Woodward Strychnine synthesis 2

1. NaCN, DMF
2. LAH, THF
3. Na₂SO₄, CHCl₃, H₂O

mechanism: step 1

mechanism: step 2
Woodward Strychnine synthesis 3

mechanism: step 1

mechanism: step 2
Woodward Strychnine synthesis 4

1. NaBH₄, EtOH, H₂O
2. Ac₂O, py.

mechanism: step 1

mechanism: step 2
Woodward Strychnine synthesis 5

1. $O_3$, HOAc
2. $Na_2SSO_3$

ozonolysis mechanism
Woodward Strychnine synthesis 6

mechanism:
Woodward Strychnine synthesis 7

1. HI, red P^o
2. Ac_2O, py.
3. CH_2N_2
4. NaOMe, MeOH

steps 1 & 2: mechanisms

step 3: mechanism

diazomethane

step 4: mechanism
Woodward Strychnine synthesis 8

1. TsCl, py.
2. PhCH₂SNa
3. Ra-Ni

step 1: mechanism

step 2: mechanism
Woodward Strychnine synthesis 9

Steps 1&2:

Step 3: mechanism
Woodward Strychnine synthesis 10

1. HCl, H_2O
2. SeO_2, EtOH

step 1: mechanism

step 2: mechanism
Woodward Strychnine synthesis 11

1. $\text{H-C=C-Na, THF}$
2. $\text{H}_2$, Pd-BaSO$_4$, quinoline (Lindlar's catalyst)
3. LAH, ether

step 1: mechanism

step 2: mechanism
Woodward Strychnine synthesis 12

1. HBr, HOAc, 120°C
2. KOH, EtOH

STRYCHNINE

step 1: mechanism

step 2: mechanism

STRYCHNINE
Kuehne: short, convergent total synthesis - [3,3]/Mannich
Mechanism of the Fisher Indole Synthesis

1. HOAc, Δ

[3,3]

1. LAH
2. Ac₂O

aspidospermidine
**Figure 1.** Retrosynthetic analysis of (−)-strychnine.

Shibasaki: 31 steps

Scheme 1

6 + 7 → 8 (E:Z = 15:7:1) 9,1% >99% ee
d
10 (OPMB)
e.f
CO2Me
CO2Me
11 (OPMB)
g.l
OTIPS
j
(>6:1)
12
TMSO
TIPS
k
l
m
n
13
OTIPS
16
O
O
17
O
O
O
15
14z
OPMB

a Key: (a) (R)-ALB (0.1 mol %), KO-t-Bu (0.09 mol %), MS 4A, THF (49 M), 91%, >99% ee; (b) 2-ethyl-2-methyl-1,3-dioxolane, catalytic TsOH; (c) LiCl, H2O, DMSO, 140 °C, 97% in two steps; (d) LDA, N-methoxy-2-(4-methoxybenzoyloxy)-N-methylacetamide, THF, −78 °C, 72% (conversion 82%); (e) NaBH3CN, TiCl4, THF−CH2Cl2, −55 °C; (f) DCC, CuCl, benzene, reflux, 70% in two steps; (g) DIBAL, CH2Cl2, −78 °C; (h) TIPSOTf, Et3N, CH2Cl2, −78 °C, 98% in two steps; (i) catalytic CSA, acetone, 62% (conversion 90%); (j) lithium 2,2,6,6-tetramethylpiperidide, TMSCl, THF, −78 °C; (k) Pd2(dba)3·CHCl3 (5 mol %), diallyl carbonate, MeCN, 90% in two steps; (l) LDA, TMSCl, THF, −78 °C; (m) aq. HCHO, Yb(OTf)3 (20 mol %), THF; (n) DBU, CH2Cl2, 57% in three steps from the mixture of regioisomers 13 (conversion 80%) (o) I2, DMAP, CH2Cl2, 89%; (p) 1-iodo-2-trimethylstannylbenzene, Pd2(dba)3·CHCl3 (5 mol %), Ph3As (20 mol %), CuI (10 mol %), DMF, quantitative; (q) SEMCl, i-Pr2NEt, CH2Cl2, quantitative; (r) 3HF·Et3N, THF, quantitative; (s) Tf2O, i-Pr2NEt, then 2,2-bis(ethylthio)ethylamine, CH2Cl2, −78 °C; (t) Zn, MeOH−aqueous NH2Cl, 77% in two steps; (u) DMTSF (5 equiv), MS 4A, CH2Cl2 (0.005 M), 86%; (v) NaBH3CN, TiCl4, THF−CH2Cl2, −78 °C, 68%; (w) 1.0 M HCl in MeOH, 55 °C; (x) Ac2O, pyridine; (y) NaOMe, MeOH; (z) TIPSCI, imidazole, DMF−CH2Cl2, 4 °C, 51% in four steps; (aa) NiCl2, NaBH4, EtOH/MeOH (4:1), 61% isolated yield after 3 times process; (bb) SO3·Py, Et3N, DMSO; (cc) 3HF·Et3N, THF 83% in two steps; (dd) NaOMe, MeOH, 40 °C; (ee) malonic acid, NaOAc, Ac2O, AcOH, 110 °C, 42% in two steps.
Shibasaki: catalytic, asymmetric Michael-type reaction


12/31 steps = protecting group manipulations

7/31 steps = redox changes

19 “wasted” steps for PG & redox manipulations

1. 1 N HCl, MeOH 55 °C
2. Ac₂O, py.
3. NaOMe, MeOH
4. TIPSCI, DMF, im.
51% 4 steps

5.2 mg

(-)-strychnine
Woodward strychnine synthesis: 1 PG for +2 steps
Kuehne strychnine synthesis: 2 PG for + 4 steps

Kuehne Synthesis: 4 changes in oxidation state

Rawal: Shortest Synthesis on Record - IMDA & Heck Reactions


15 steps
~10% overall yield
Funk Analysis

7 rings
1 basic N
1 seven-membered ring
1 alkene
1 quaternary center
6 stereogenic centers
17 points = 34 steps maximum

<table>
<thead>
<tr>
<th>Investigator</th>
<th># of Steps</th>
<th>Overall Yield</th>
<th>Year</th>
<th>Enantioselective?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woodward</td>
<td>28</td>
<td>&lt;0.001%</td>
<td>1954</td>
<td>Racemic</td>
</tr>
<tr>
<td>Magnus</td>
<td>27</td>
<td>0.03%</td>
<td>1992</td>
<td>Racemic</td>
</tr>
<tr>
<td>Kuehne</td>
<td>17</td>
<td>2%</td>
<td>1993</td>
<td>Racemic</td>
</tr>
<tr>
<td>Rawal</td>
<td>15</td>
<td>10%</td>
<td>1994</td>
<td>Racemic</td>
</tr>
<tr>
<td>Overman</td>
<td>25</td>
<td>3%</td>
<td>1995</td>
<td>Enantioselective</td>
</tr>
<tr>
<td>Shibasaki</td>
<td>31</td>
<td>0.67%</td>
<td>2002</td>
<td>Enantioselective</td>
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</table>
A database tool for process chemists and chemical engineers to gauge the material and synthetic efficiencies of synthesis plans to industrially important targets

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Abstract: After 20 years of green chemistry research, a complete algorithm for the determination of material and synthetic strategy efficiencies for synthesis plans to any chemical target has been achieved. This paper presents the first announcement of a comprehensive database consisting of green metrics calculations for 1060 plans to 220 targets of interest to the chemical industry in the following categories: commodity industrial chemicals, pharmaceuticals, agrichemicals, dyestuffs and colorants, natural products, flavorings, fragrances, and sweeteners, and molecules of theoretical interest. Data mining of the original literature covered the period 1828–2010. A summary of trends in achieving green chemistry strategies is presented, including an unbiased method of ranking plans using a suite of parameters, ring construction strategies, and implications on the development of new kinds of smart structure search databases. The take-home message is that targeted optimization is a multivariable problem that requires synergistic maximization and minimization of key variables. Problems in the reporting of chemical syntheses in scientific journals and patents are discussed as well as setting guidelines for their standardization and normalization. The merits of spreadsheet tools are presented from decision making in route selection all the way to fast and accurate proofreading of the final plan chosen.
Table 8. Summary of Metrics for Syntheses of Strychnine Arranged in Ascending Order of Kernel Waste Production

<table>
<thead>
<tr>
<th>Plan</th>
<th>Year</th>
<th>Type</th>
<th>Na</th>
<th>M</th>
<th>Rc</th>
<th>$\mu_1$</th>
<th>$\beta$</th>
<th>$\delta$</th>
<th>f(sac)</th>
<th>B/M</th>
<th>HII</th>
<th>% Yield</th>
<th>% AE</th>
<th>% RME</th>
<th>Kernel Mass of Waste (kg)</th>
</tr>
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<tbody>
<tr>
<td>Rawal</td>
<td>1994</td>
<td>convergent</td>
<td>14</td>
<td>20</td>
<td>34</td>
<td>-126.25</td>
<td>0.893</td>
<td>0.422</td>
<td>0.699</td>
<td>0.80</td>
<td>+1.67</td>
<td>33.1</td>
<td>7.8</td>
<td>2.2</td>
<td>16.1</td>
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<td>Bodwell</td>
<td>2002</td>
<td>convergent</td>
<td>15</td>
<td>19</td>
<td>30</td>
<td>-43.45</td>
<td>0.880</td>
<td>0.394</td>
<td>0.691</td>
<td>0.68</td>
<td>+0.81</td>
<td>2.9</td>
<td>9.8</td>
<td>1.0</td>
<td>33.4</td>
</tr>
<tr>
<td>Kuehne</td>
<td>1993</td>
<td>convergent</td>
<td>20</td>
<td>23</td>
<td>38</td>
<td>-34.96</td>
<td>0.927</td>
<td>0.372</td>
<td>0.683</td>
<td>0.61</td>
<td>+2.53</td>
<td>2.3</td>
<td>7.6</td>
<td>0.4</td>
<td>84.9</td>
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<tr>
<td>Padwa</td>
<td>2007</td>
<td>convergent</td>
<td>17</td>
<td>21</td>
<td>36</td>
<td>-6.26</td>
<td>0.938</td>
<td>0.386</td>
<td>0.657</td>
<td>0.67</td>
<td>+3.89</td>
<td>1.6</td>
<td>9.0</td>
<td>0.4</td>
<td>89.8</td>
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<td>Overman</td>
<td>1995</td>
<td>convergent</td>
<td>26</td>
<td>28</td>
<td>50</td>
<td>-0.50</td>
<td>0.952</td>
<td>0.365</td>
<td>0.653</td>
<td>0.79</td>
<td>+3.37</td>
<td>1.5</td>
<td>6.0</td>
<td>0.3</td>
<td>111.6</td>
</tr>
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<td>Fukuyama</td>
<td>2004</td>
<td>convergent</td>
<td>25</td>
<td>29</td>
<td>50</td>
<td>+59.20</td>
<td>0.952</td>
<td>0.371</td>
<td>0.753</td>
<td>0.72</td>
<td>+4.73</td>
<td>1.1</td>
<td>5.2</td>
<td>0.3</td>
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<td>Martin</td>
<td>2001</td>
<td>convergent</td>
<td>16</td>
<td>18</td>
<td>29</td>
<td>-63.55</td>
<td>0.917</td>
<td>0.369</td>
<td>0.719</td>
<td>0.78</td>
<td>+3.35</td>
<td>0.8</td>
<td>12.5</td>
<td>0.2</td>
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</tr>
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<td>Vollhardt</td>
<td>2001</td>
<td>convergent</td>
<td>14</td>
<td>19</td>
<td>28</td>
<td>-90.92</td>
<td>0.871</td>
<td>0.397</td>
<td>0.676</td>
<td>0.68</td>
<td>+0.6</td>
<td>0.6</td>
<td>10.2</td>
<td>0.2</td>
<td>218.1</td>
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<td>Shibasaki</td>
<td>2004</td>
<td>linear</td>
<td>31</td>
<td>31</td>
<td>53</td>
<td>+128.53</td>
<td>0.955</td>
<td>0.346</td>
<td>0.776</td>
<td>0.52</td>
<td>+1.31</td>
<td>0.5</td>
<td>5.2</td>
<td>0.1</td>
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<tr>
<td>Mori</td>
<td>2003</td>
<td>convergent</td>
<td>24</td>
<td>28</td>
<td>50</td>
<td>+71.21</td>
<td>0.945</td>
<td>0.379</td>
<td>0.770</td>
<td>0.61</td>
<td>+0.08</td>
<td>0.3</td>
<td>5.4</td>
<td>0.04</td>
<td>785.3</td>
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<tr>
<td>Bonjoch</td>
<td>2000</td>
<td>convergent</td>
<td>18</td>
<td>22</td>
<td>39</td>
<td>-6.54</td>
<td>0.938</td>
<td>0.389</td>
<td>0.713</td>
<td>0.73</td>
<td>+6.32</td>
<td>0.1</td>
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<tr>
<td>Magnus</td>
<td>1993</td>
<td>linear</td>
<td>33</td>
<td>33</td>
<td>60</td>
<td>+97.54</td>
<td>0.955</td>
<td>0.355</td>
<td>0.830</td>
<td>0.58</td>
<td>+4.09</td>
<td>0.003</td>
<td>4.4</td>
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<tr>
<td>Woodward</td>
<td>1963</td>
<td>convergent</td>
<td>29</td>
<td>30</td>
<td>45</td>
<td>+38.18</td>
<td>0.939</td>
<td>0.334</td>
<td>0.768</td>
<td>0.80</td>
<td>+3.47</td>
<td>5e-5</td>
<td>9.8</td>
<td>2e-5</td>
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<tr>
<td>Stork</td>
<td>1992</td>
<td>convergent</td>
<td>16</td>
<td>20</td>
<td>33</td>
<td>+26.64</td>
<td>0.874</td>
<td>0.400</td>
<td>0.755</td>
<td>0.60</td>
<td>+2.53</td>
<td>&lt;100</td>
<td>10.4</td>
<td>&lt;6</td>
<td>&gt;5.2</td>
</tr>
</tbody>
</table>

a Number of reaction stages, b Number of reaction steps, c Number of input materials, d Molecular weight first moment building up parameter, e Degree of asymmetry, f Degree of convergence, g Fraction of sacrificial reagents by molecular weight, h Number of target bonds made per reaction step, i Hypsacity index, j Basis is 1 mole of strychnine target product