Supplementary Information: EvolvedComplexity as a Total Synthesis Assessment Metric: Strychnine as a Case Study of Scoring Functions

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1.0 Computational Details

1.1 Scoring Function Calculation

Eighteen syntheses of Strychnine were curated from Synarchive.com, an online platform that hosts a comprehensive collection of organic syntheses.[1] For each synthesis, the structures of all intermediates were extracted and converted into SMILES strings. Existing scoring functions - graph-based, complexity-based, and reaction-based - were applied to these structures using publicly available implementations on their respective GitHub repositories.[1] Complexity scores were calculated for each structure within the synthetic pathway across all 18 syntheses of Strychnine. After computing the scores for all intermediates, the values were normalized to a scale of 0 to 1 for each scoring function of each synthesis. These normalized scores were then plotted and visualized using Microsoft Excel.

The Evolved Complexity (EC) score was determined using Tanimoto Similarity, implemented via RDKit.[2] Tanimoto similarities were calculated as the distance between each intermediate and the final target molecule (Strychnine). Like the traditional scoring functions, all Tanimoto similarities (ECscore) were normalized between 0 and 1 for each synthesis. A free online tool providing access to the ECscore and the other top-performing scoring functions can be found at www.ec-scores.com.

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[1] https://github.com/connorcoley/scscore (For SCScore)
https://github.com/lich-uct/nonpher (For Bertz, Whitlock, Barone, SMCM Scores)
https://github.com/reymond-group/RAscore (For RAscore)
https://github.com/forlilab/bottchscore (Böttcher Score)
SAscore, SPS, and nSPS were implemented via the RDKit package

2.0 Strychnine Syntheses

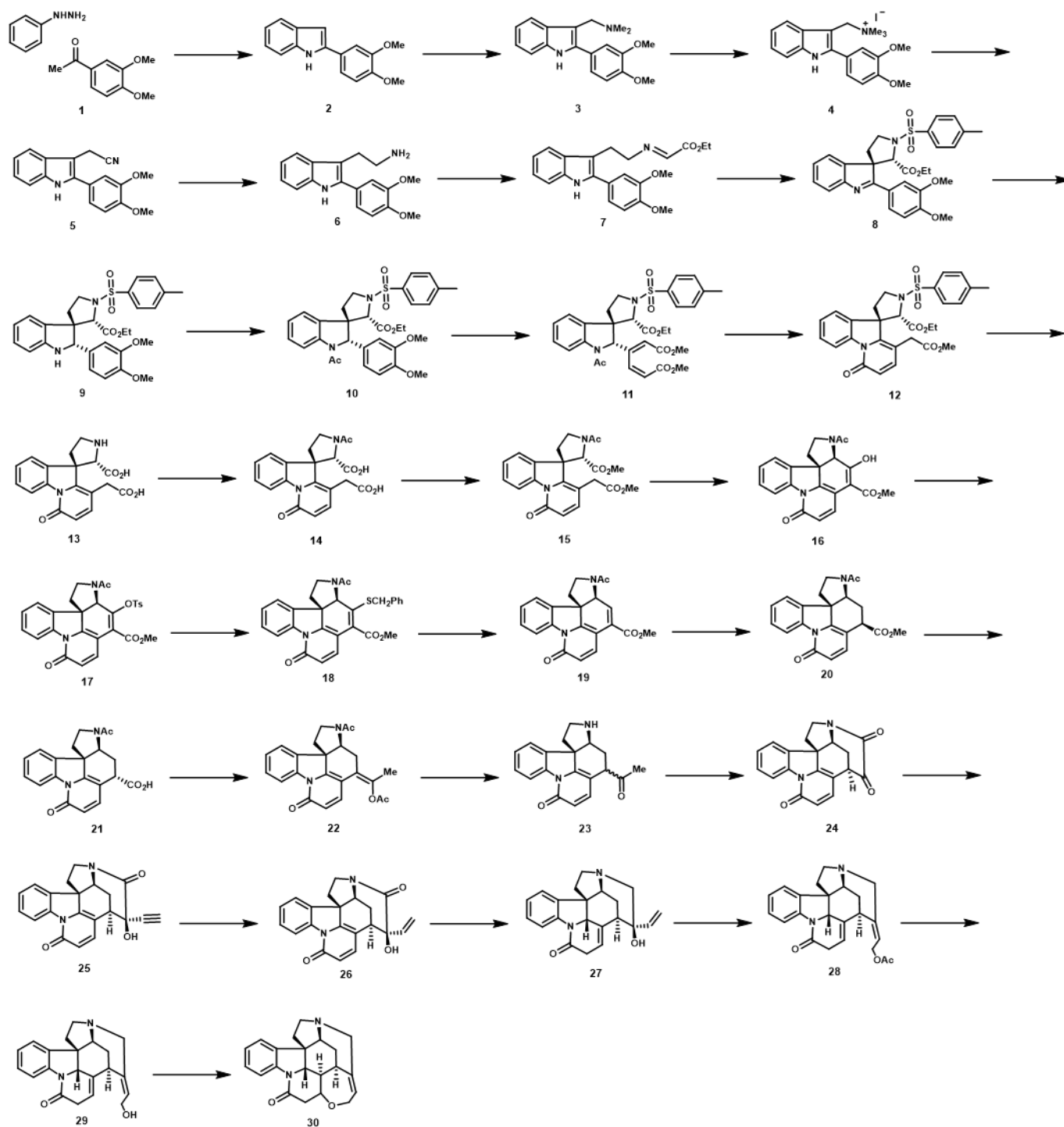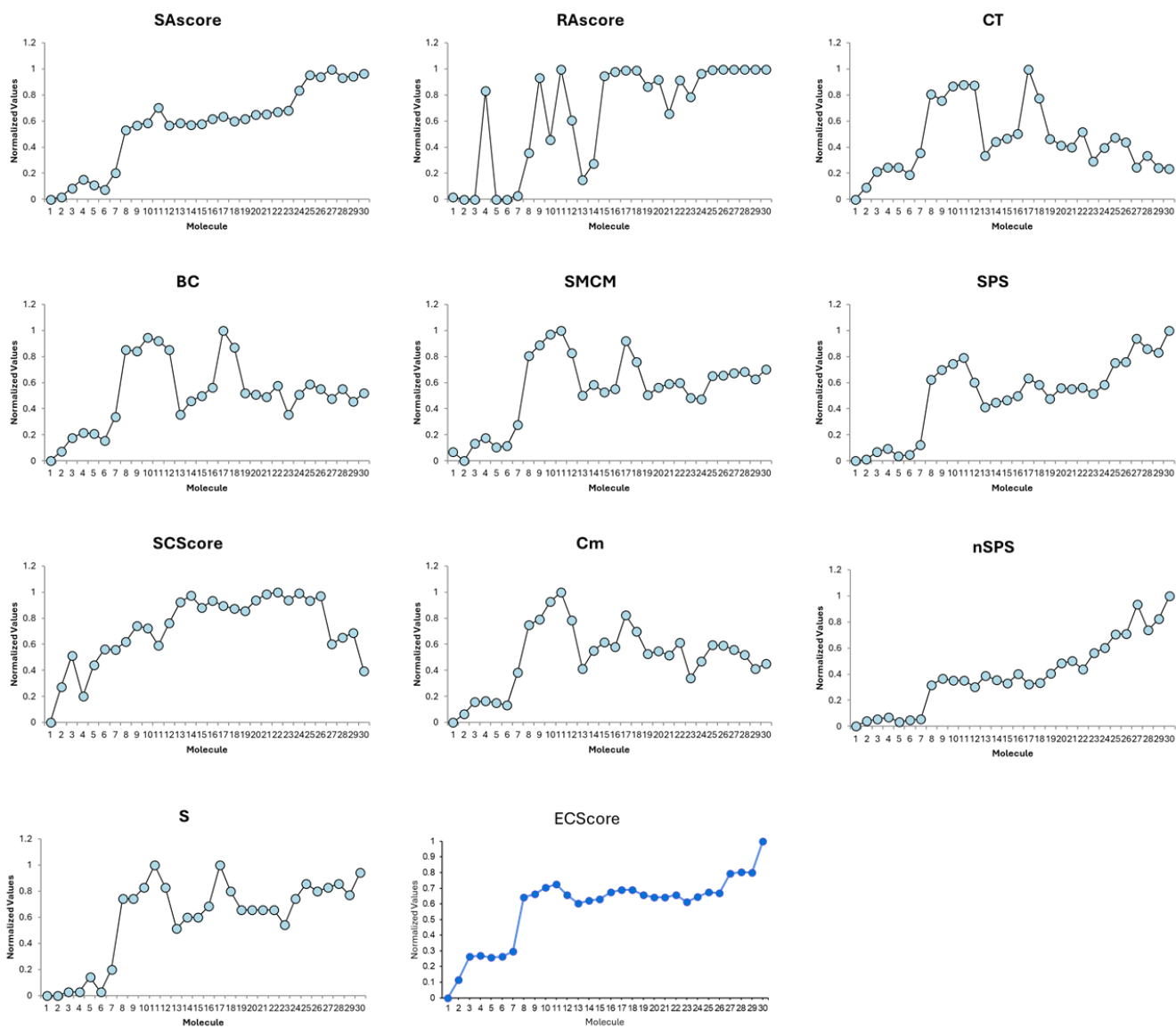## 1.1 Woodward (1954)[3]

Figure S1. Woodward's 1954 synthesis of Strychnine.

Figure S2. Scoring functions performance on Woodward's 1954 synthesis of Strychnine. Values were normalized between 0 and 1. Scoring function represented in the graph is indicated in the title of the plot.
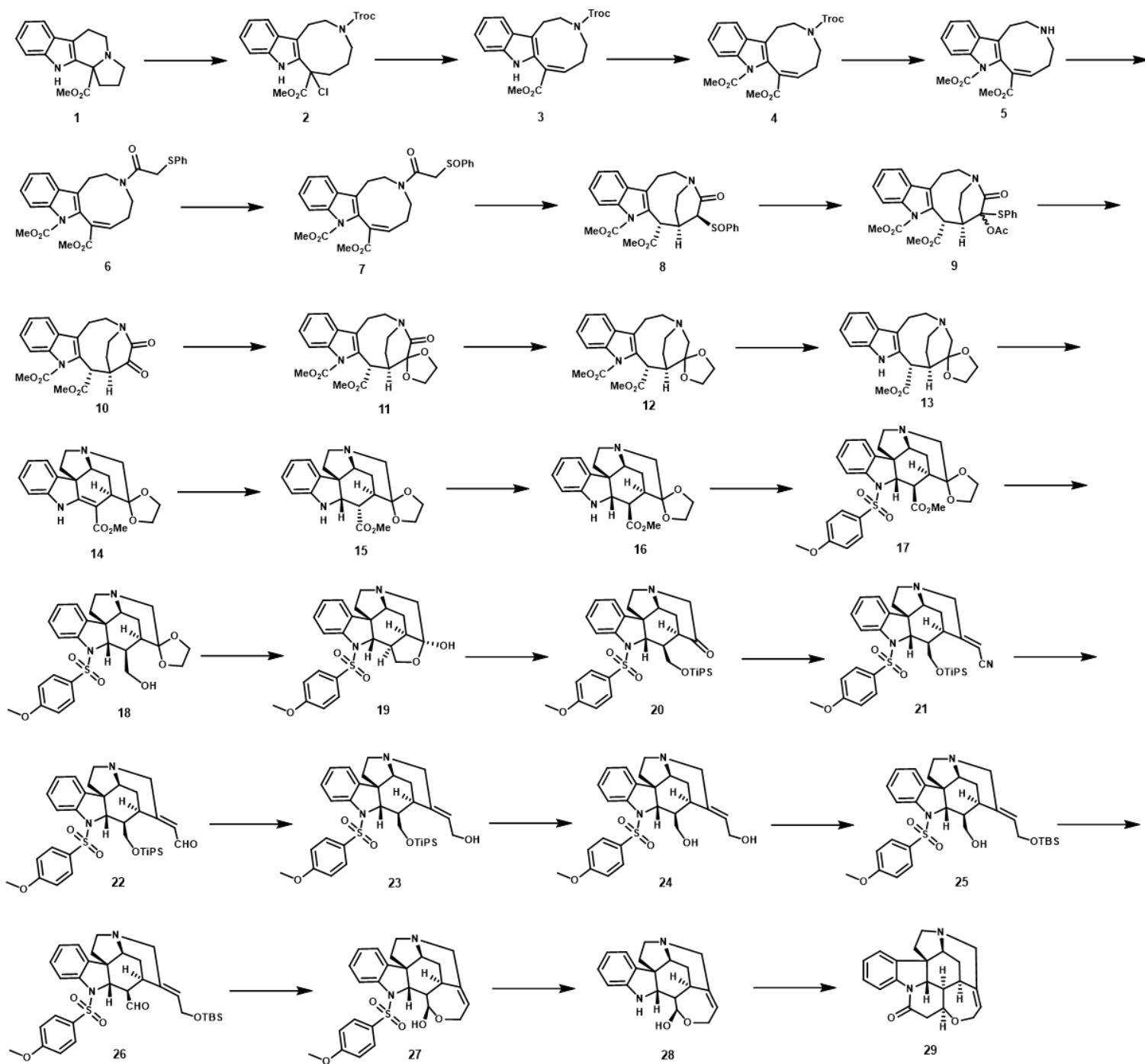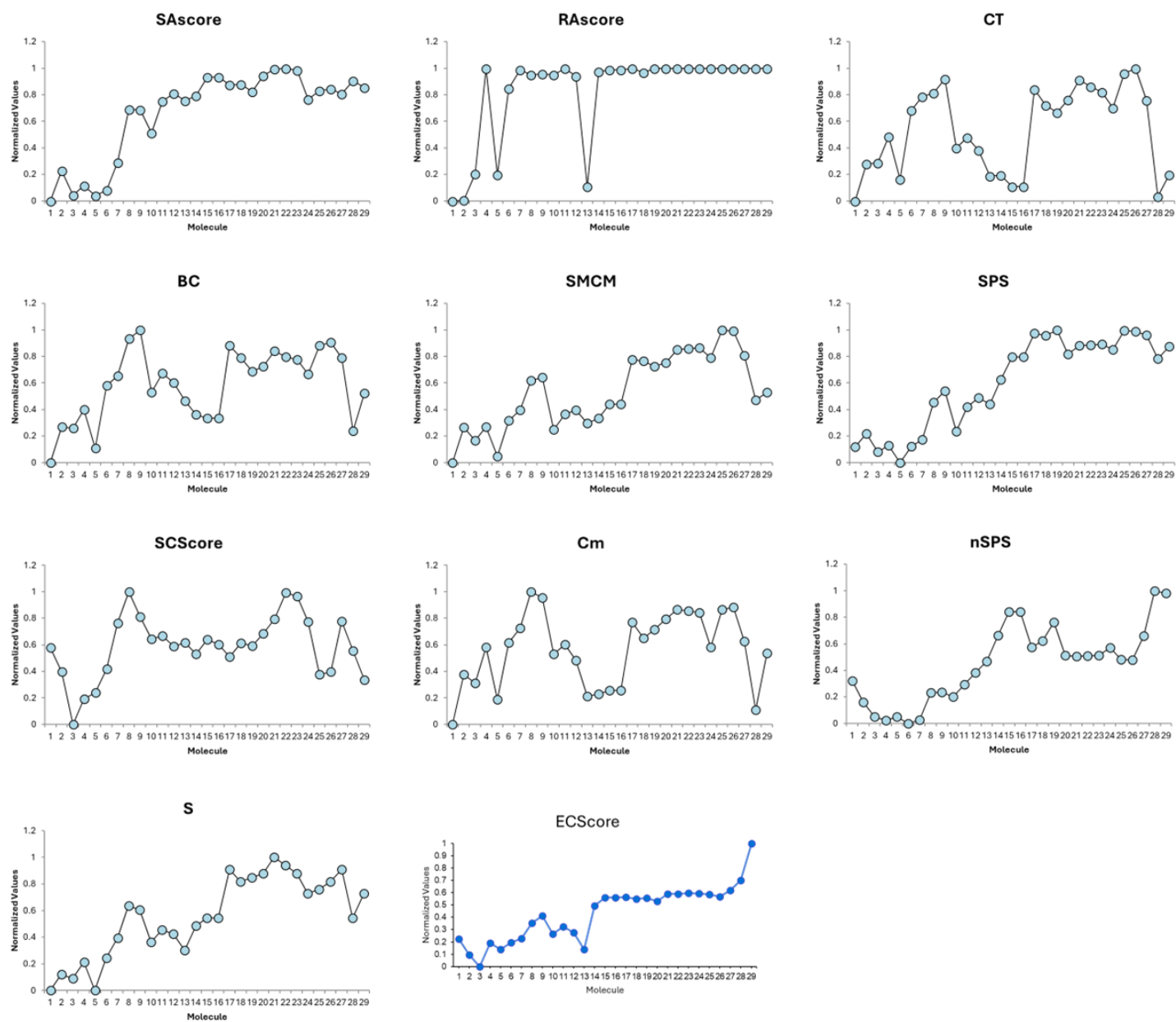
1.2 Magnus (1993)[4]

Figure S3. Magnus' 1992 synthesis of Strychnine.

Figure S4. Scoring functions performance on Magnus' 1993 synthesis of Strychnine. Values were normalized between 0 and 1. Scoring function represented in the graph is indicated in the title of the plot.
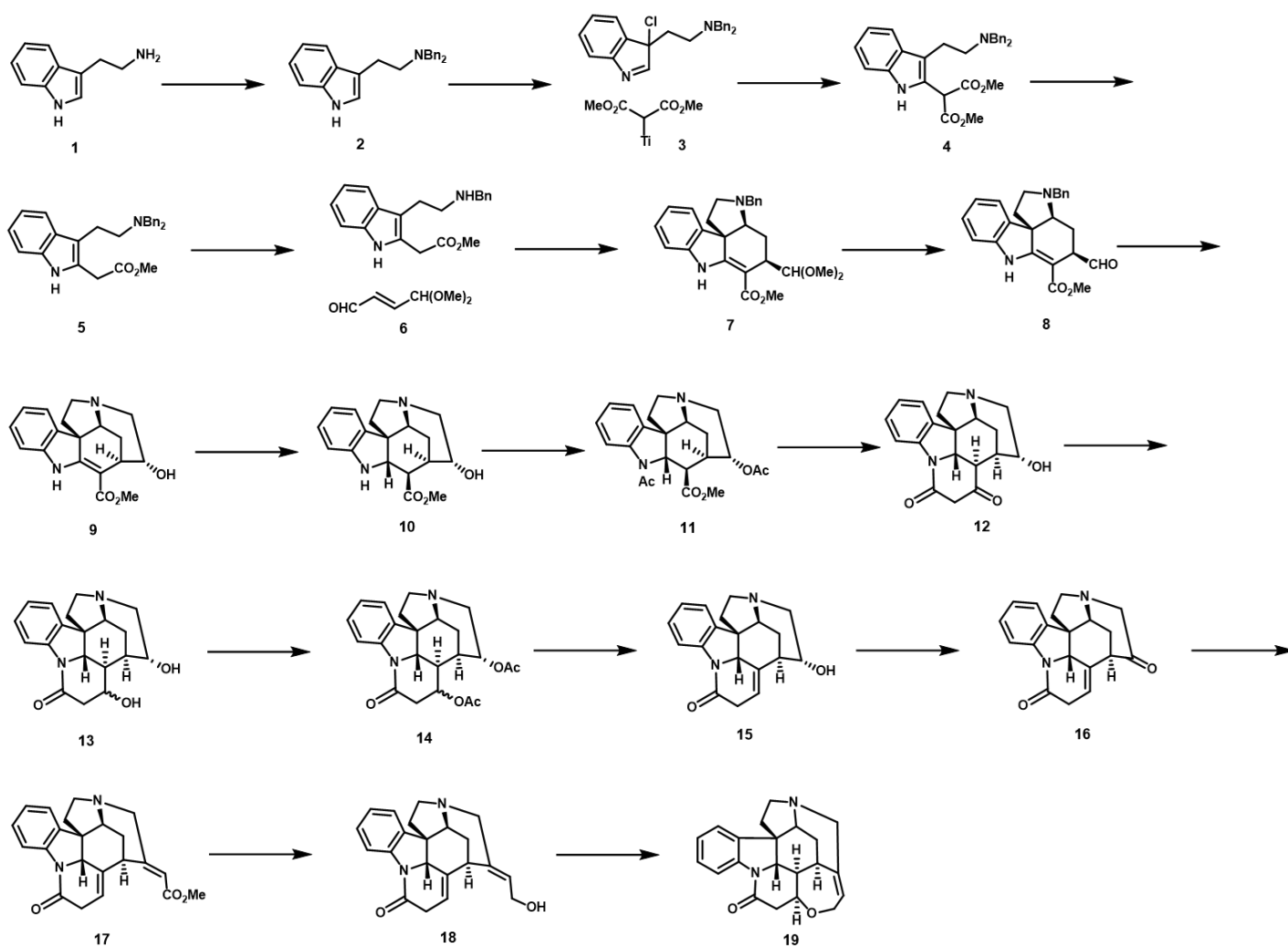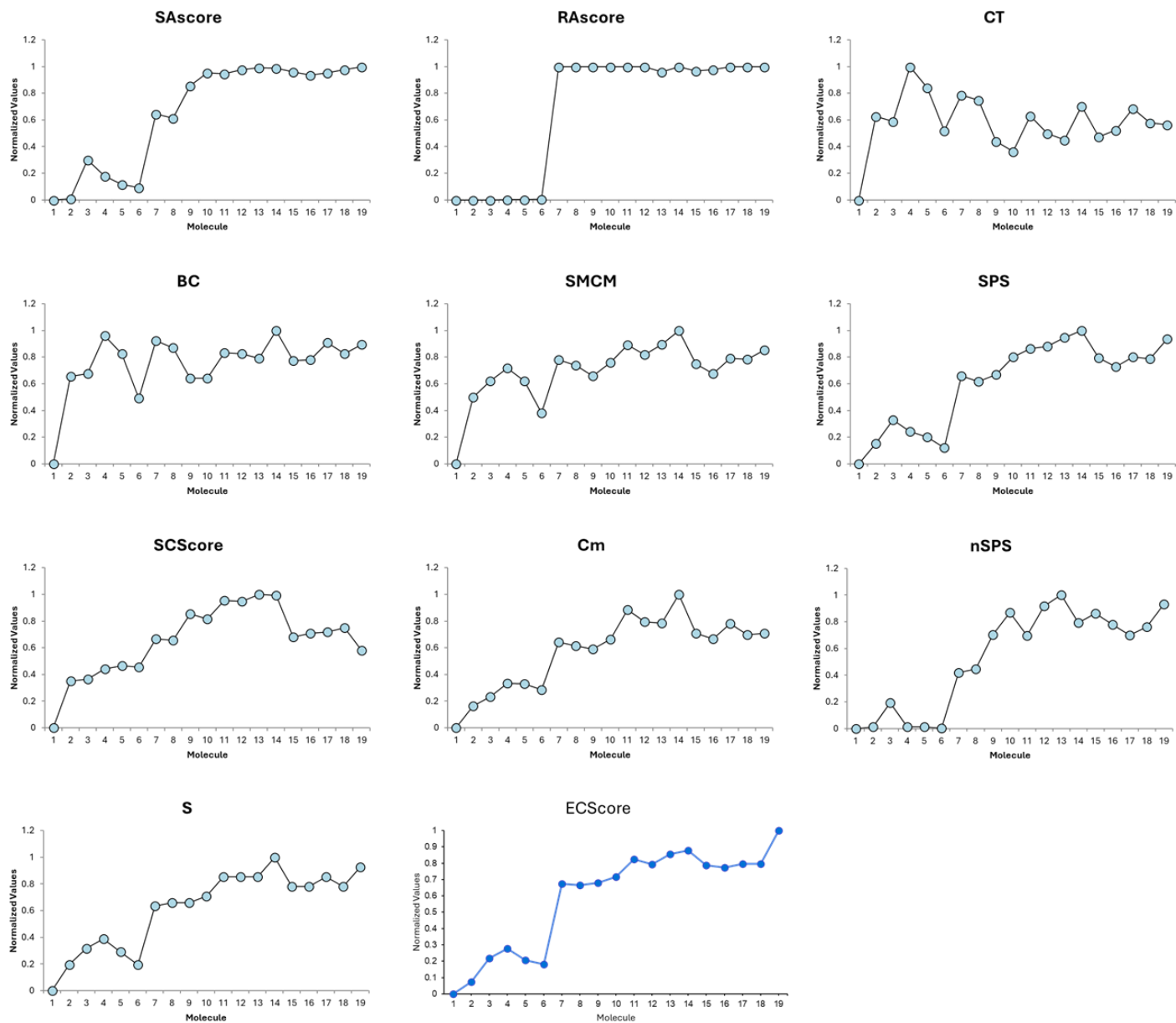
1.3 Kuehne (1993)[5]

Figure S5. Kuehne's 1993 synthesis of Strychnine.

Figure S6. Scoring functions performance on Kuehne's 1993 synthesis of Strychnine. Values were normalized between 0 and 1. Scoring function represented in the graph is indicated in the title of the plot.
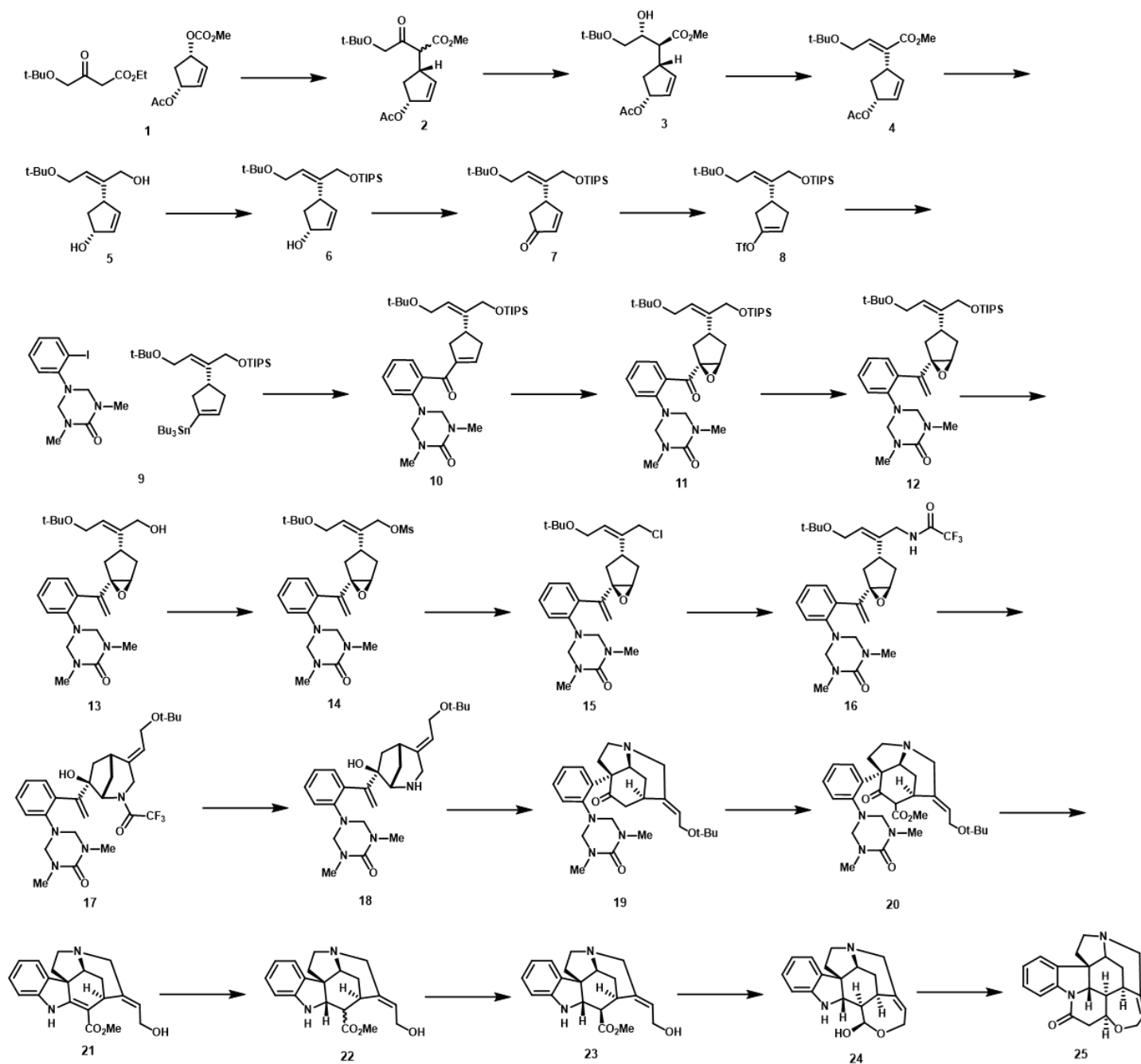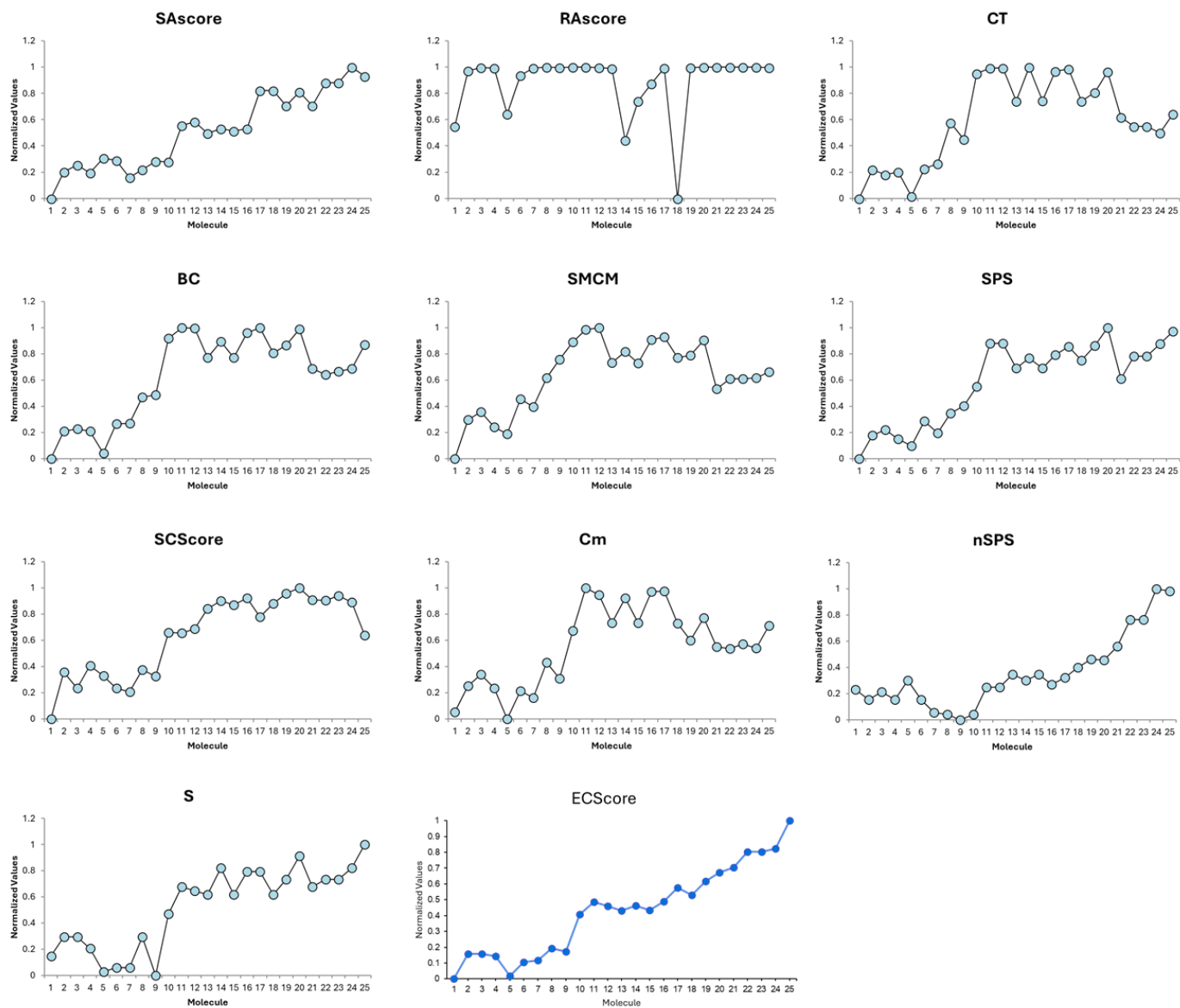
1.4 Overman (1994)[6]

Figure S7. Overman's 1994 synthesis of Strychnine.

Figure S8. Scoring functions performance on Overman's 1994 synthesis of Strychnine. Values were normalized between 0 and 1. Scoring function represented in the graph is indicated in the title of the plot.
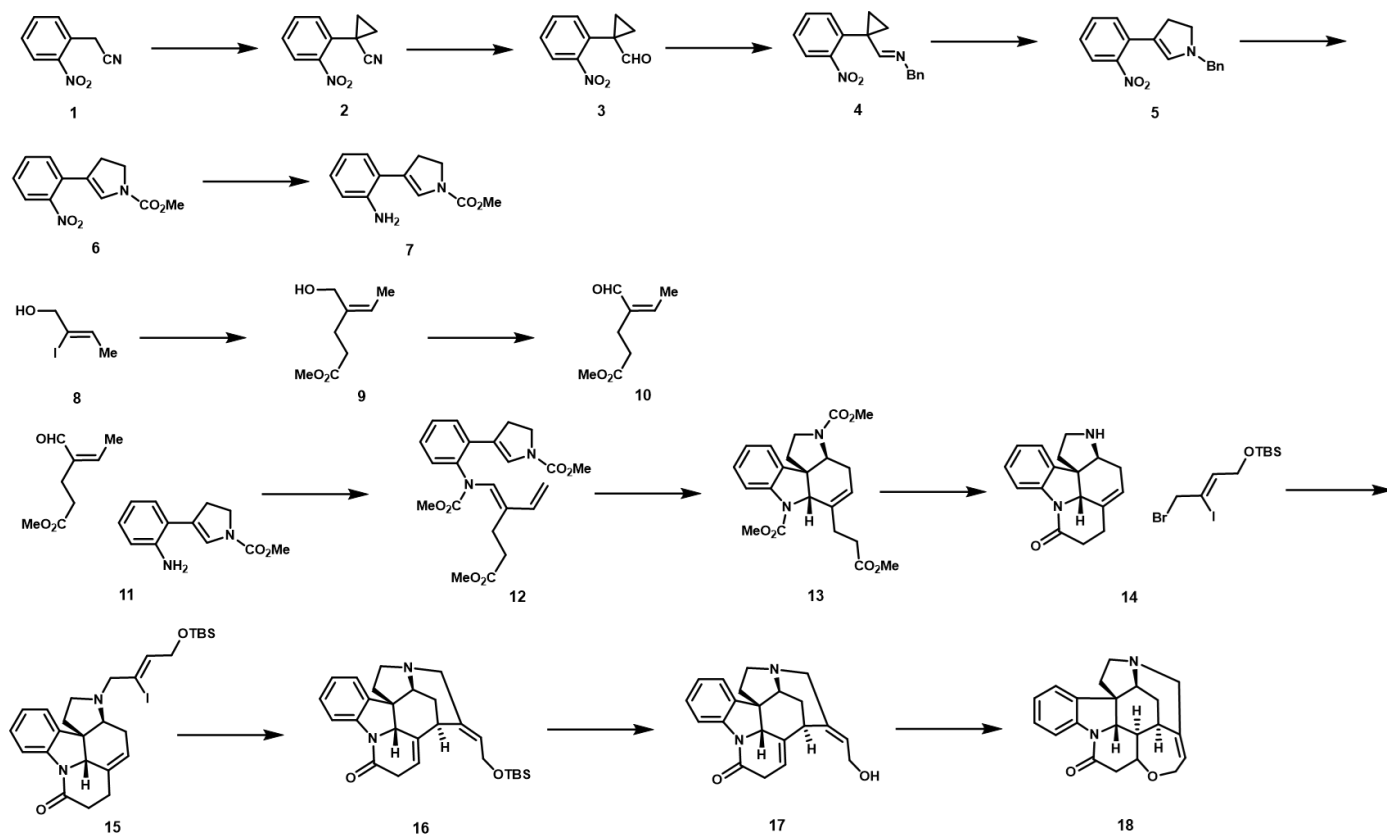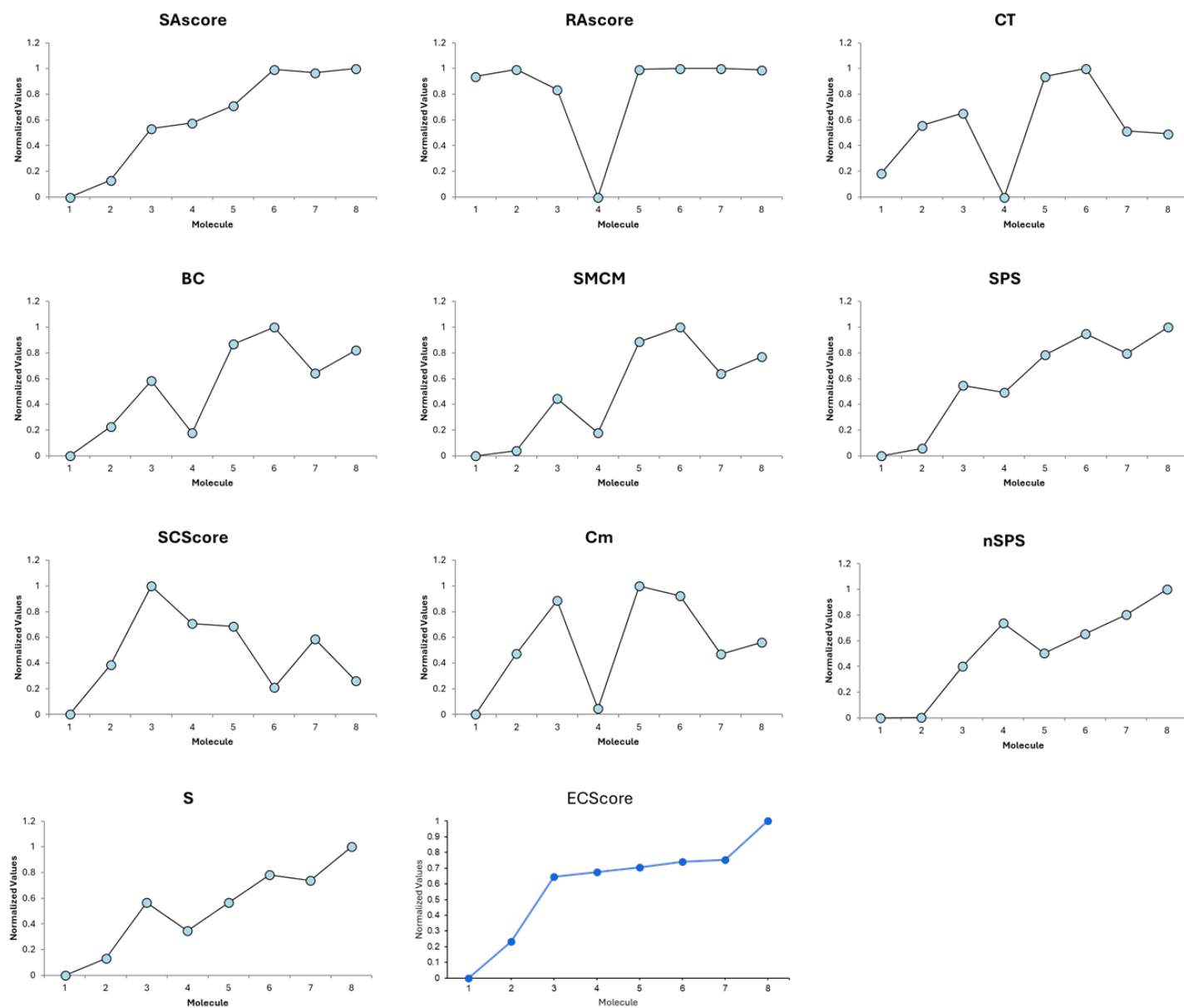
1.5 Rawal (1994)[7]

Figure S9. Rawal's 1994 synthesis of Strychnine.

Figure S10. Scoring functions performance on Rawal's 1994 synthesis of Strychnine. Values were normalized between 0 and 1. Scoring function represented in the graph is indicated in the title of the plot.
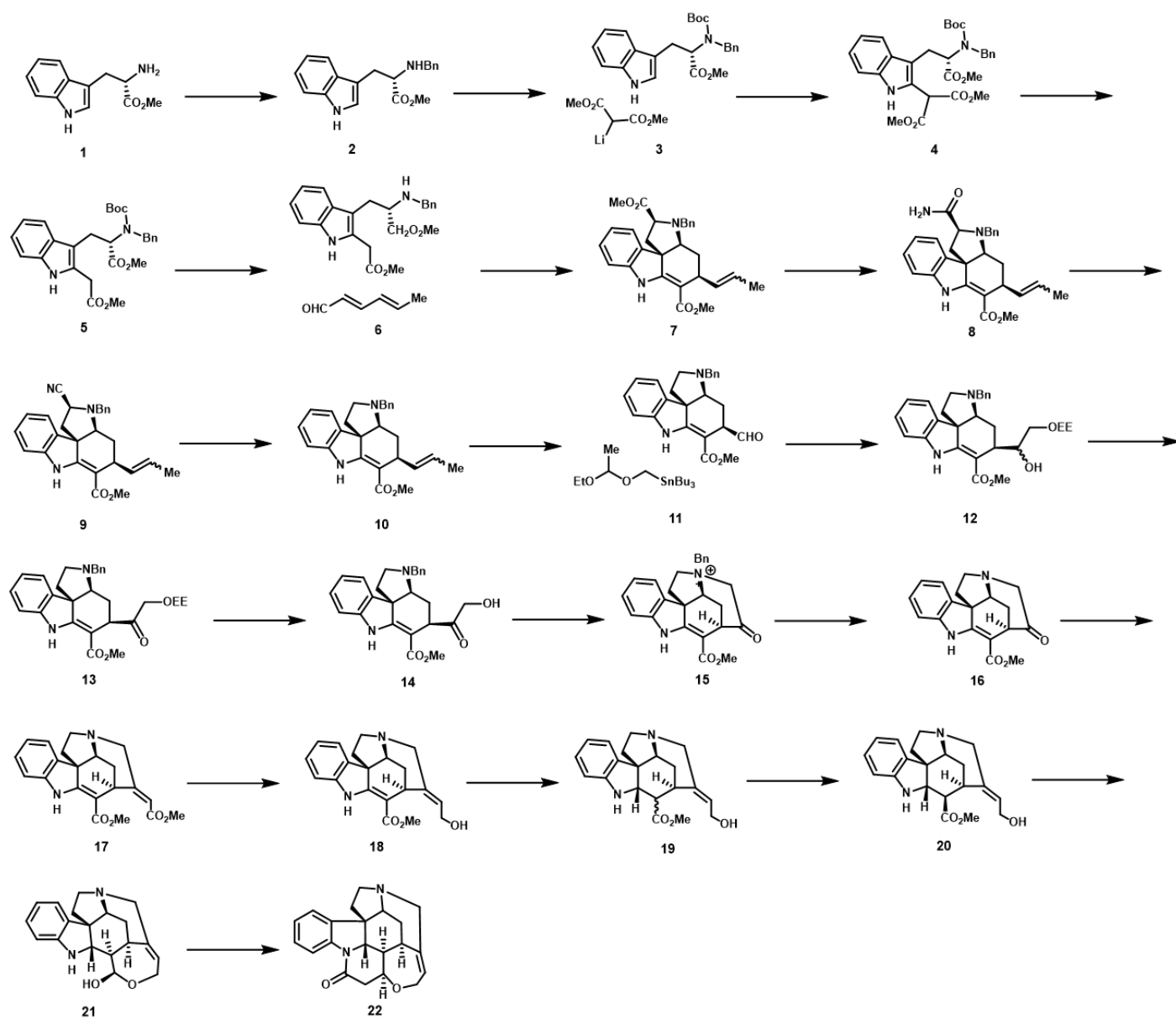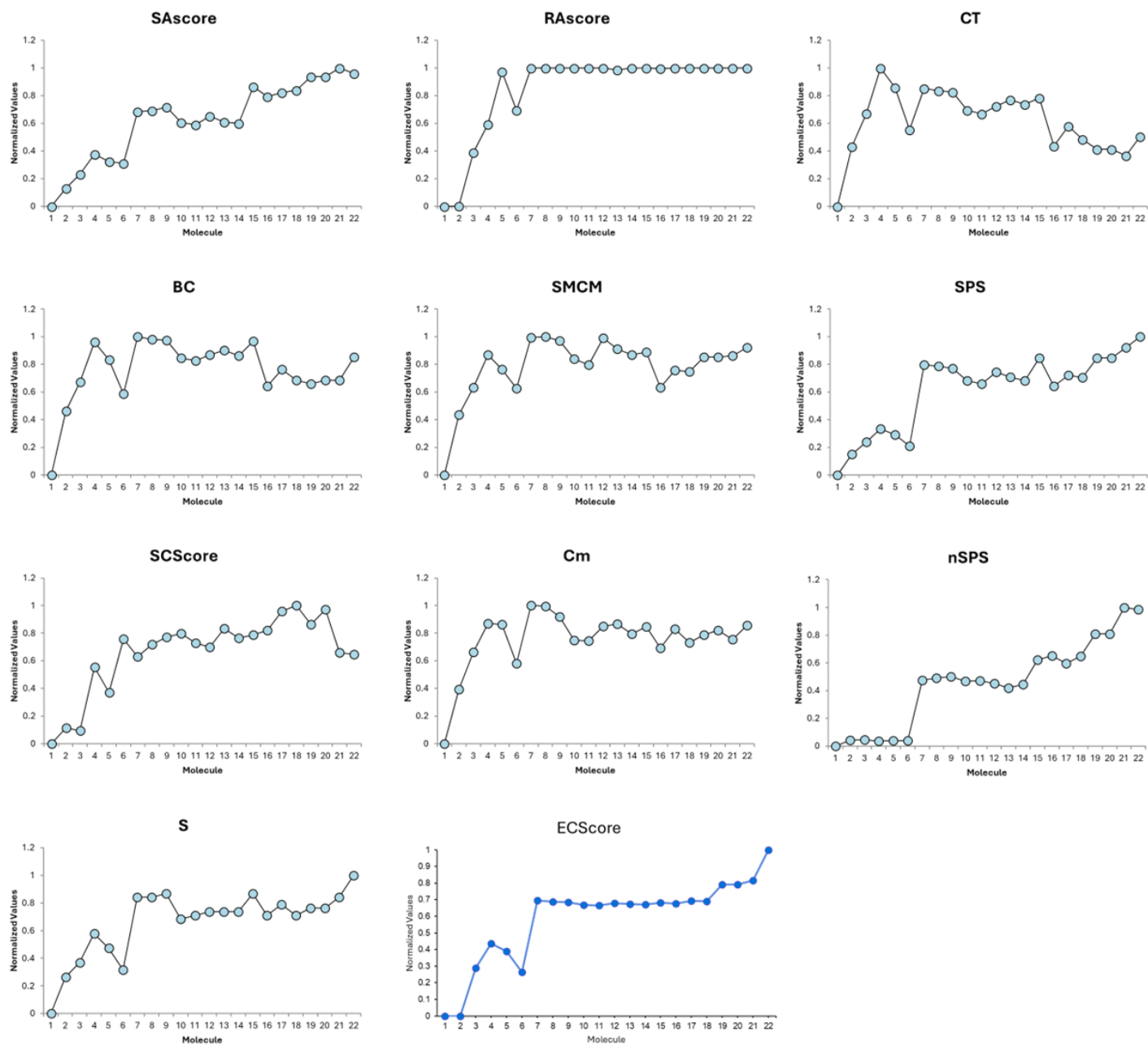
1.6 Kuehne (1998)[8]

Figure S11. Kuehne's 1998 synthesis of Strychnine.

Figure S12. Scoring functions performance on Kuehne's 1998 synthesis of Strychnine. Values were normalized between 0 and 1. Scoring function represented in the graph is indicated in the title of the plot.
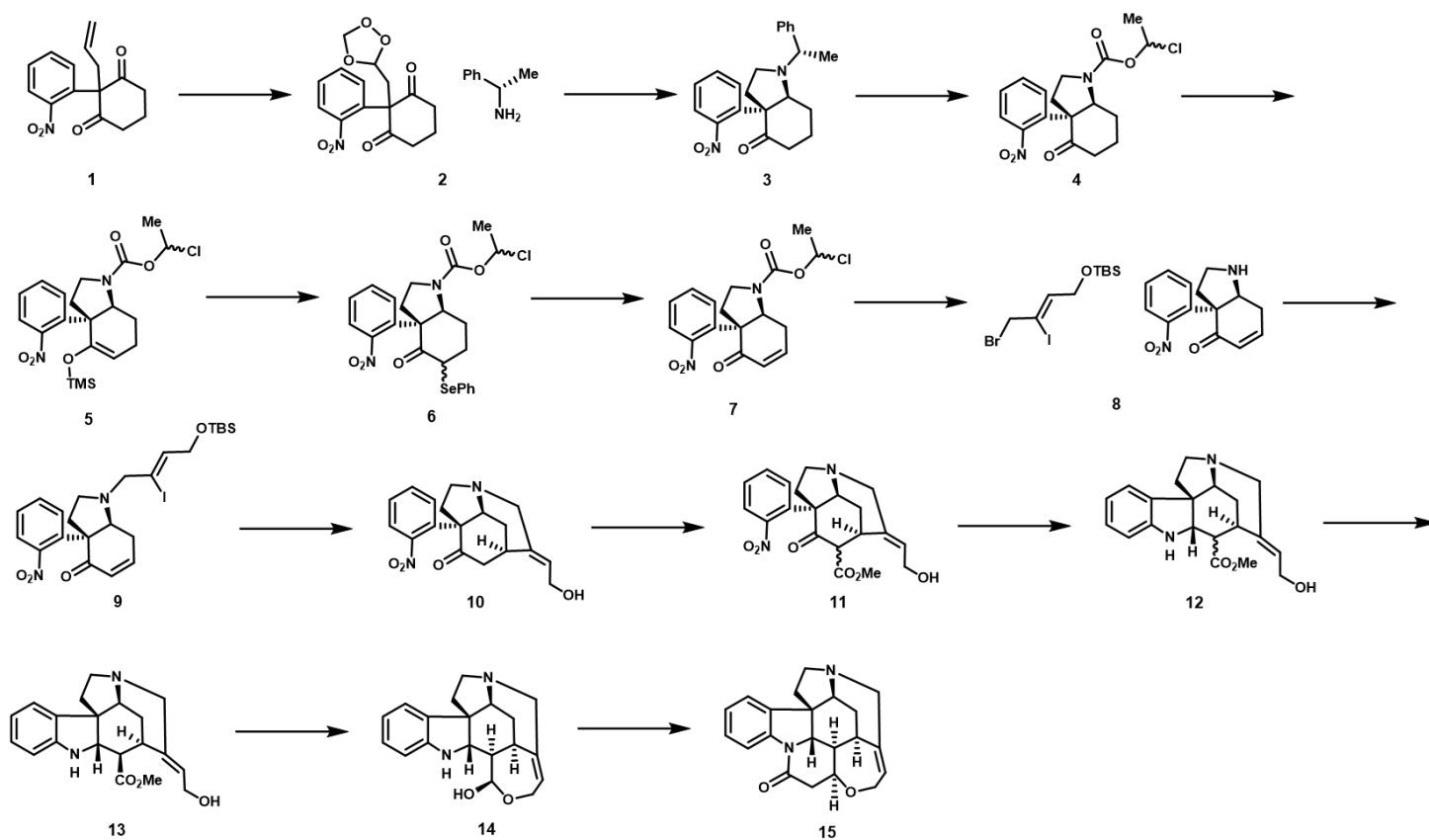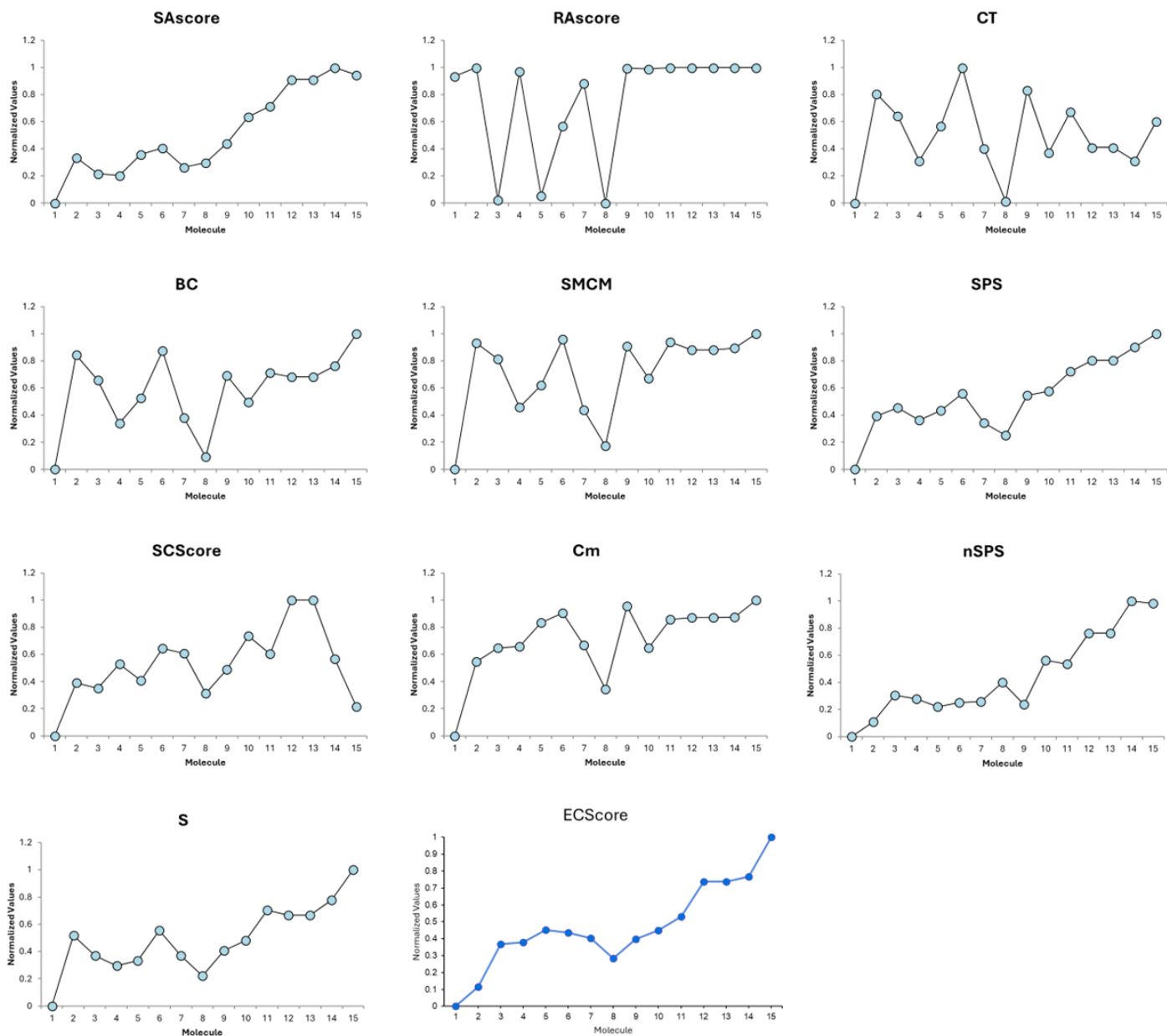
1.7 Bosch (2000)[9, 10]

Figure S13. Bosch's 2000 synthesis of Strychnine.

Figure S14. Scoring functions performance on Bosch's 2000 synthesis of Strychnine. Values were normalized between 0 and 1. Scoring function represented in the graph is indicated in the title of the plot.
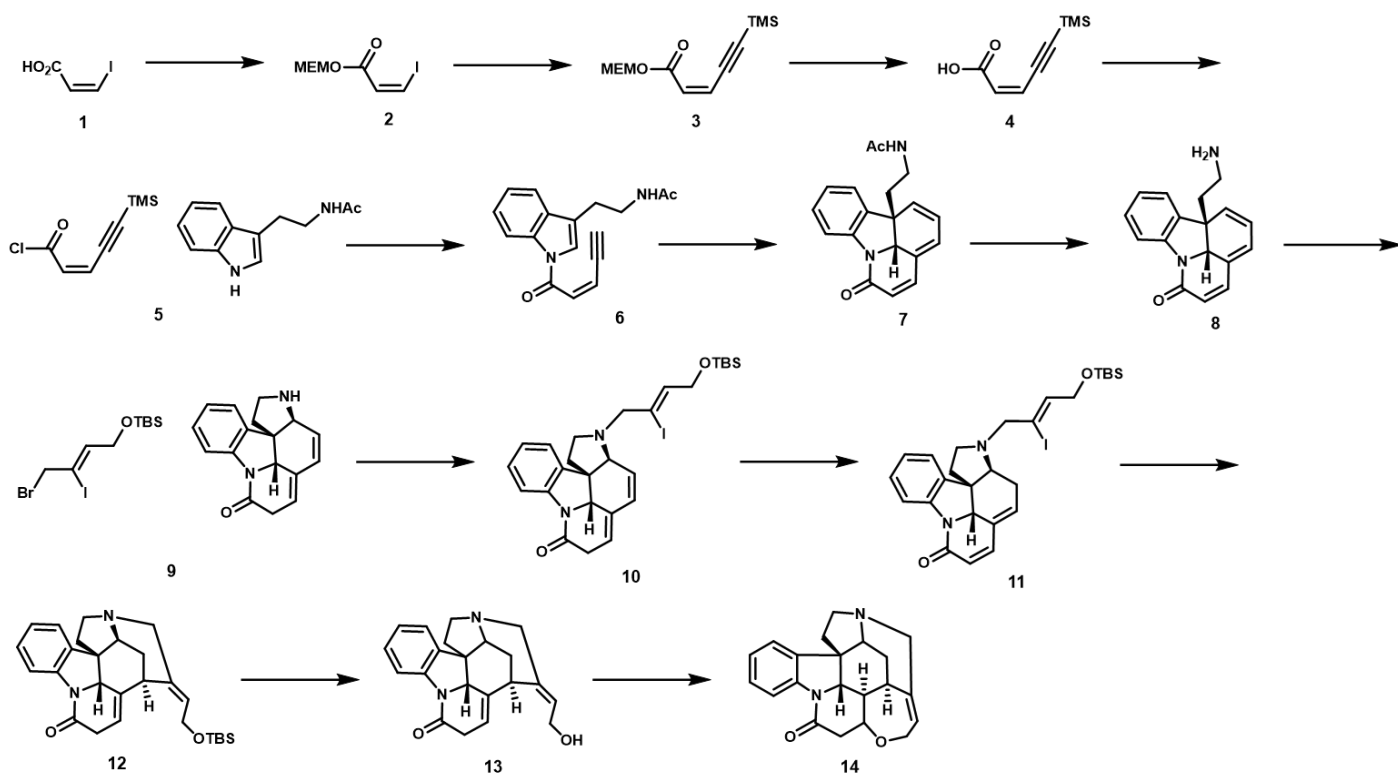
Figure S15. Volhardt's 2000 synthesis of Strychnine.

Figure S16. Scoring functions performance on Volhardt's 2000 synthesis of Strychnine. Values were normalized between 0 and 1. Scoring function represented in the graph is indicated in the title of the plot.

1.9 Martin (2001)[13]

Figure S17. Martin's 2001 synthesis of Strychnine.

Figure S18. Scoring functions performance on Martin's 2001 synthesis of Strychnine. Values were normalized between 0 and 1. Scoring function represented in the graph is indicated in the title of the plot.

1.10   Bodwell (2002)[14]

Figure S19. Bodwell's 2002 synthesis of Strychnine.

Figure S20. Scoring functions performance on Bodwell's synthesis of Strychnine. Values were normalized between 0 and 1. Scoring function represented in the graph is indicated in the title of the plot.
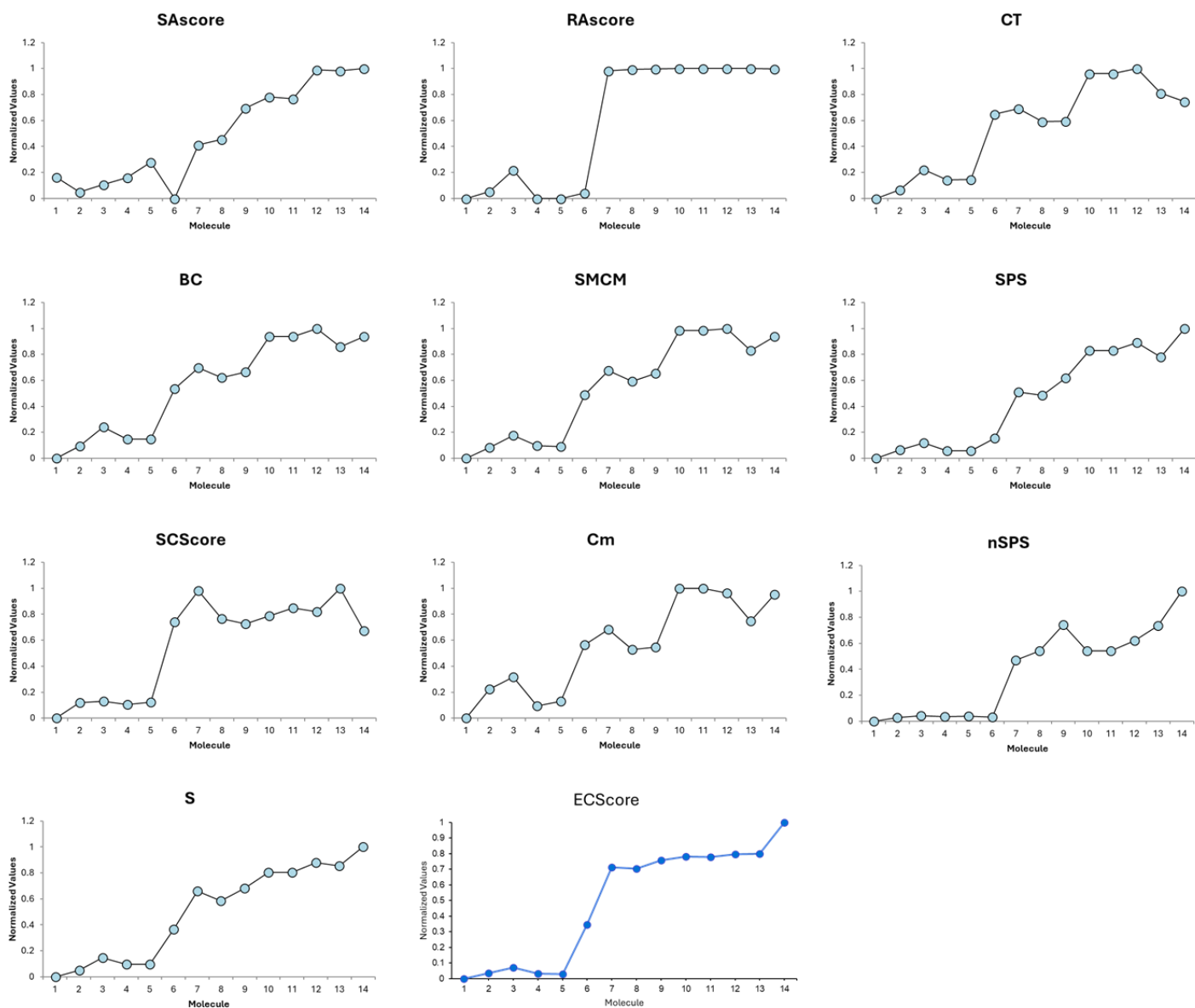
1.11   Shibasaki (2002)[15, 16]

Figure S21. Shibasaki's 2002 synthesis of Strychnine.

Figure S22. Scoring functions performance on Shibasaki's 2002 synthesis of Strychnine. Values were normalized between 0 and 1. Scoring function represented in the graph is indicated in the title of the plot.
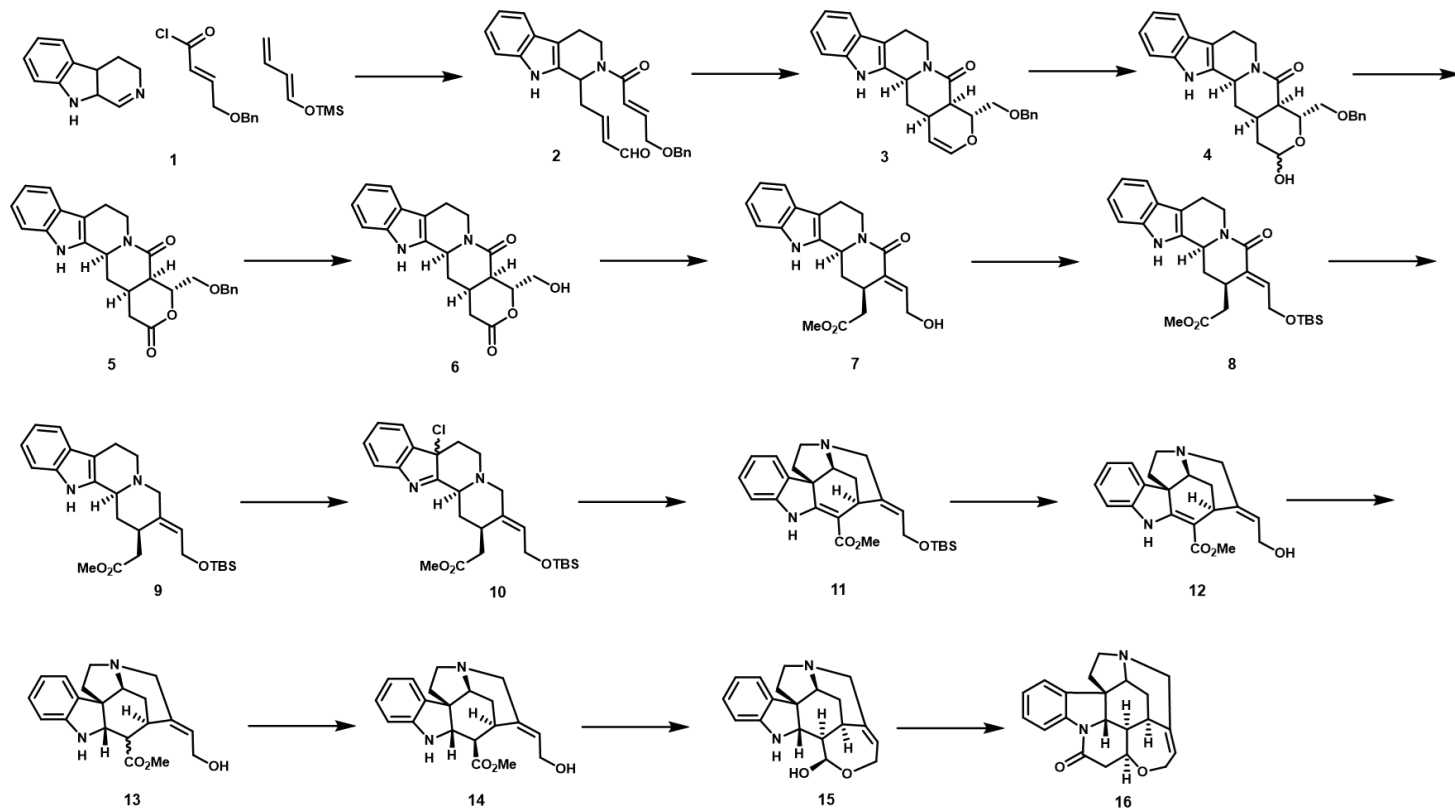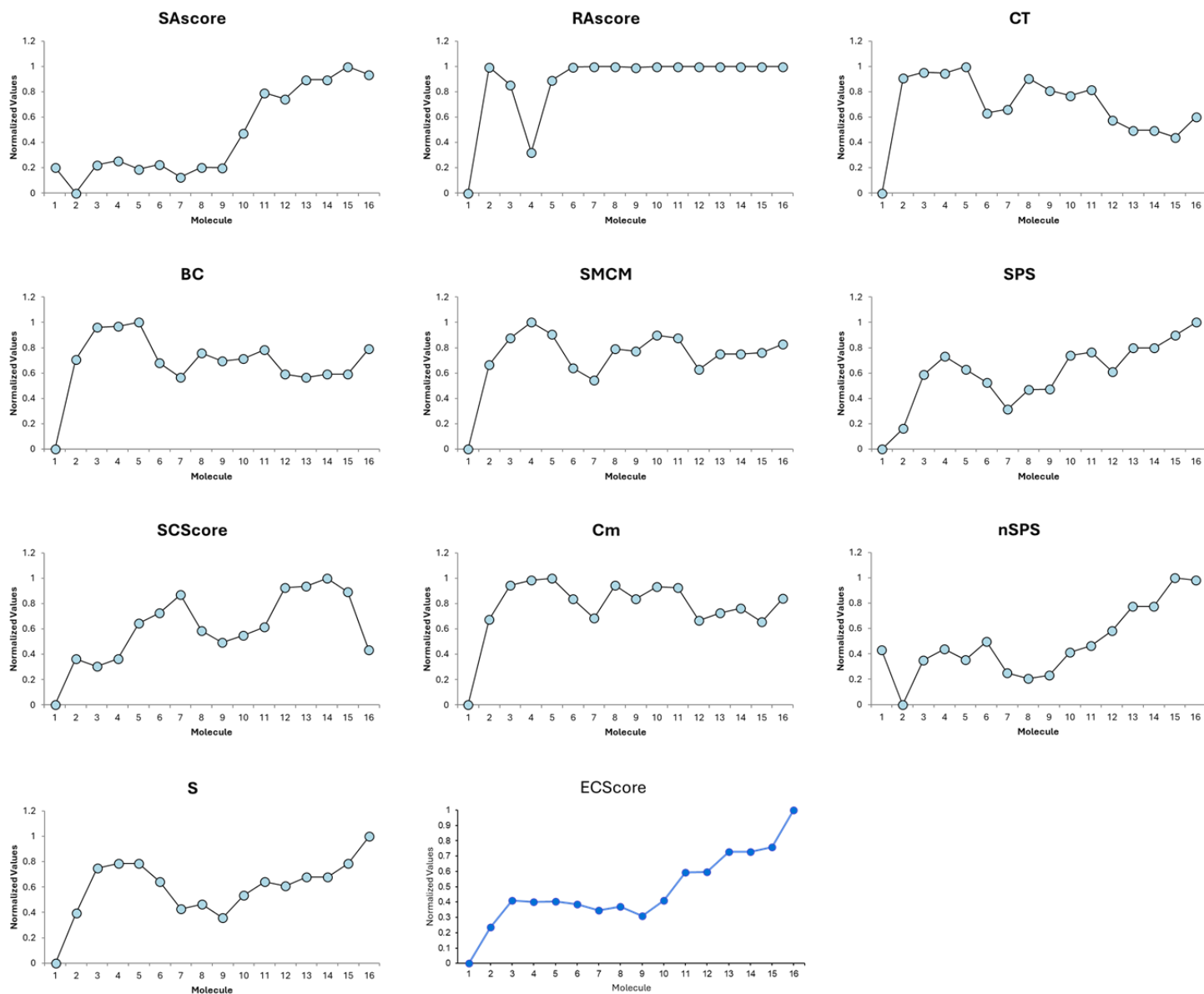
1.12   Mori (2003)[17-19]

Figure S23. Mori's 2003 synthesis of Strychnine.

Figure S24. Scoring functions performance on Mori's 2003 synthesis of Strychnine. Values were normalized between 0 and 1. Scoring function represented in the graph is indicated in the title of the plot.

1.13   Fukuyama (2004)[20]
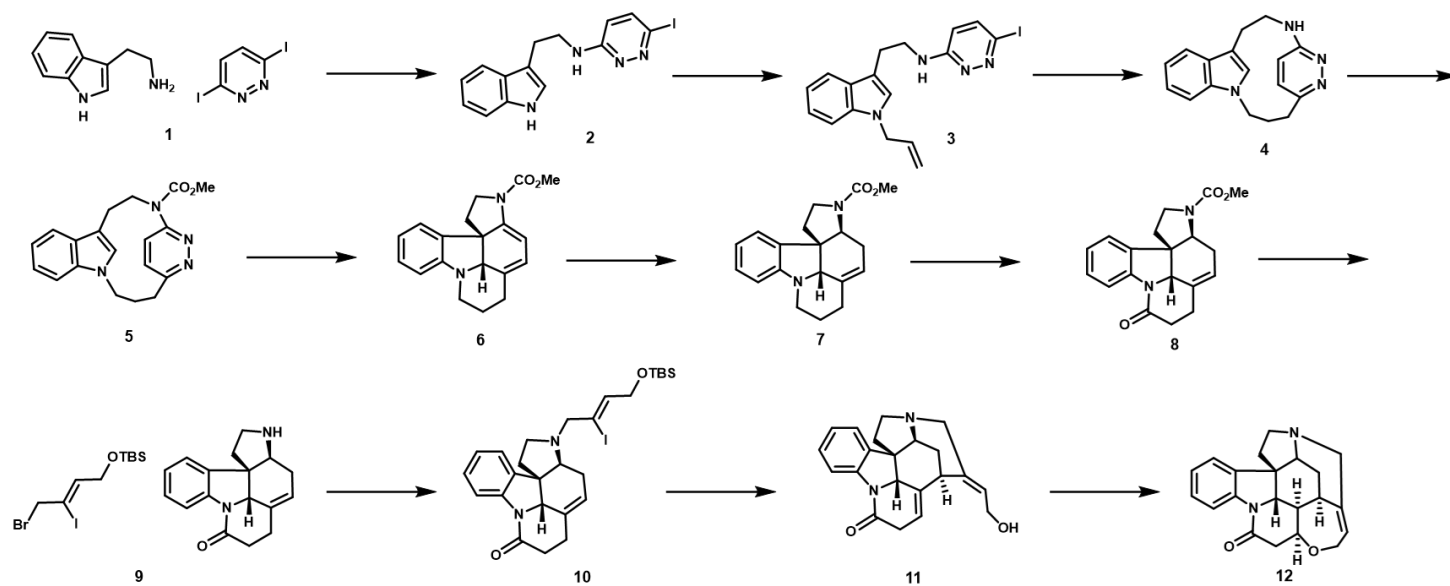

Figure S25. Fukuyama's 2004 synthesis of Strychnine.

Figure S26. Scoring functions performance on Fukuyama's 2004 synthesis of Strychnine. Values were normalized between 0 and 1. Scoring function represented in the graph is indicated in the title of the plot.
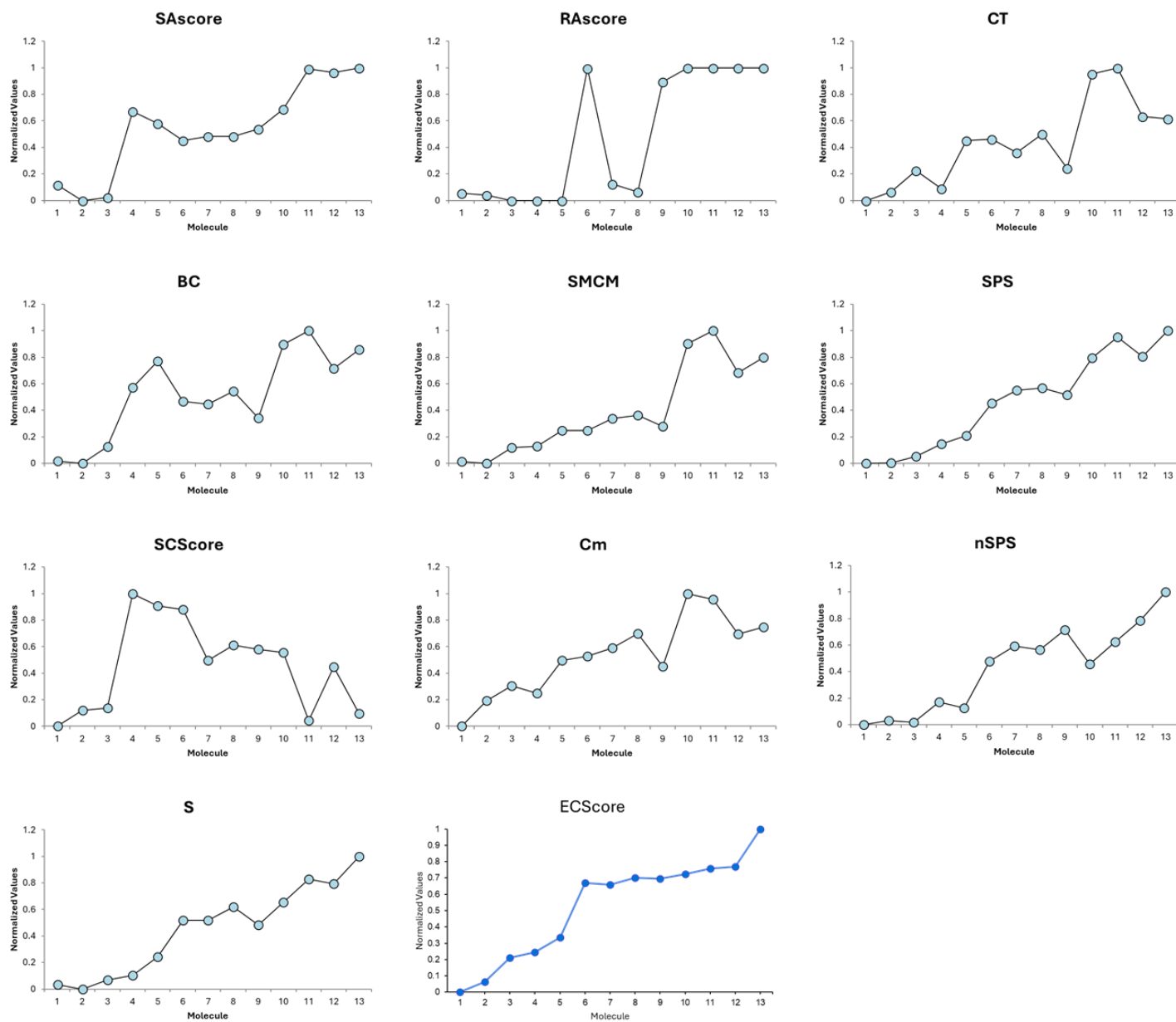
1.14 Padwa (2007)[21]
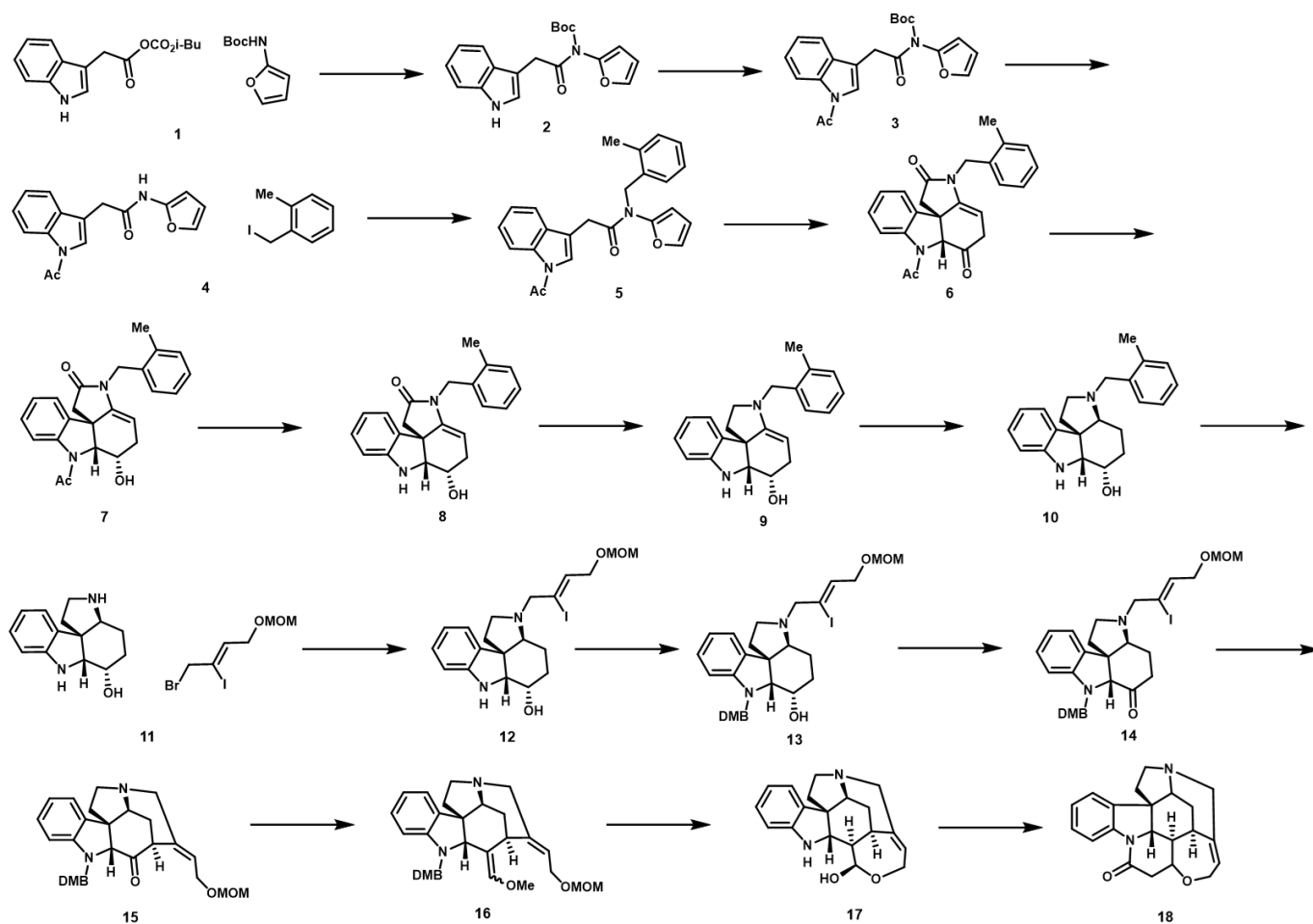
Figure S27. Padwa's 2007 synthesis of Strychnine.
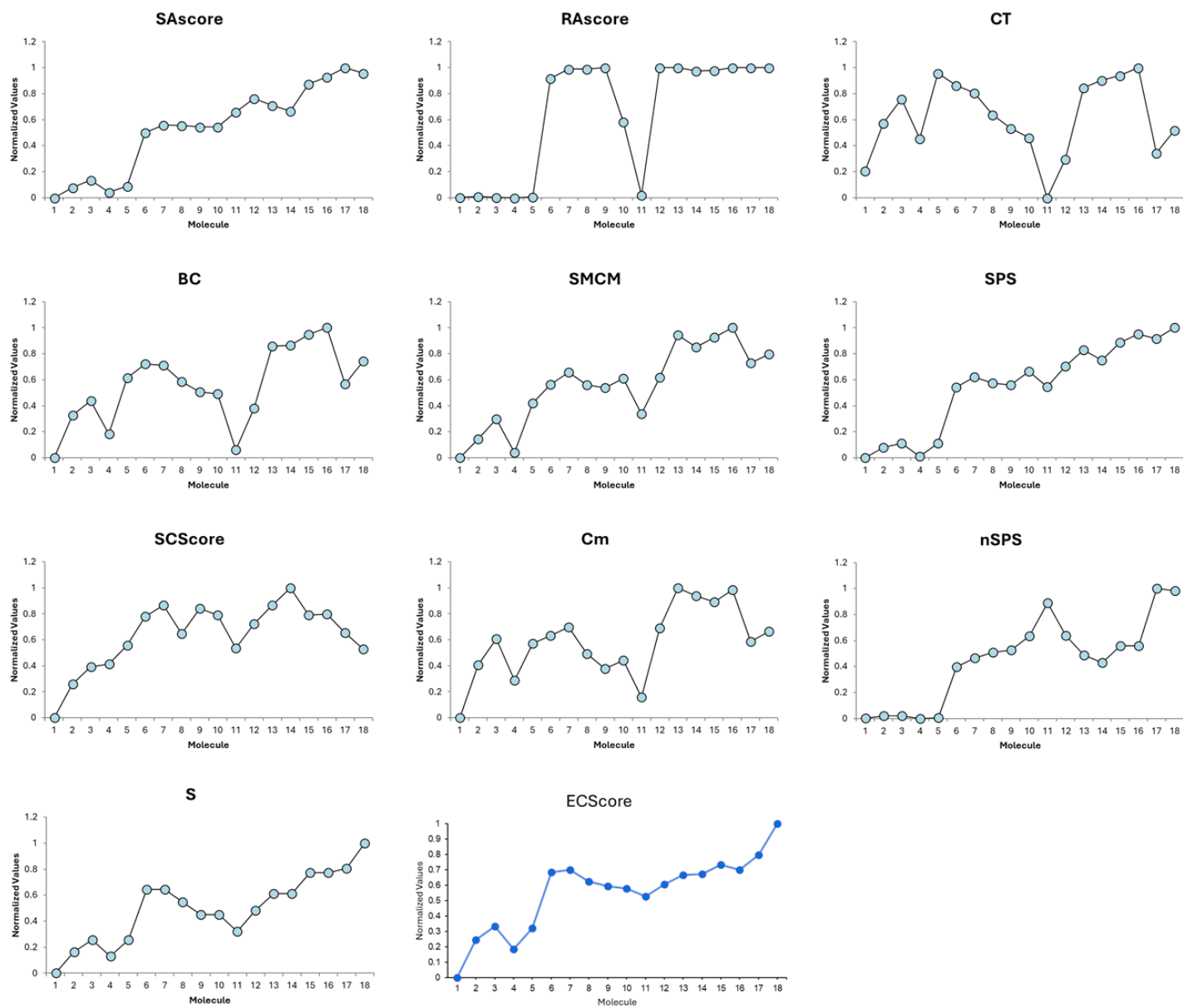
Figure S28. Scoring functions performance on Padwa's 2007 synthesis of Strychnine. Values were normalized between 0 and 1. Scoring function represented in the graph is indicated in the title of the plot.
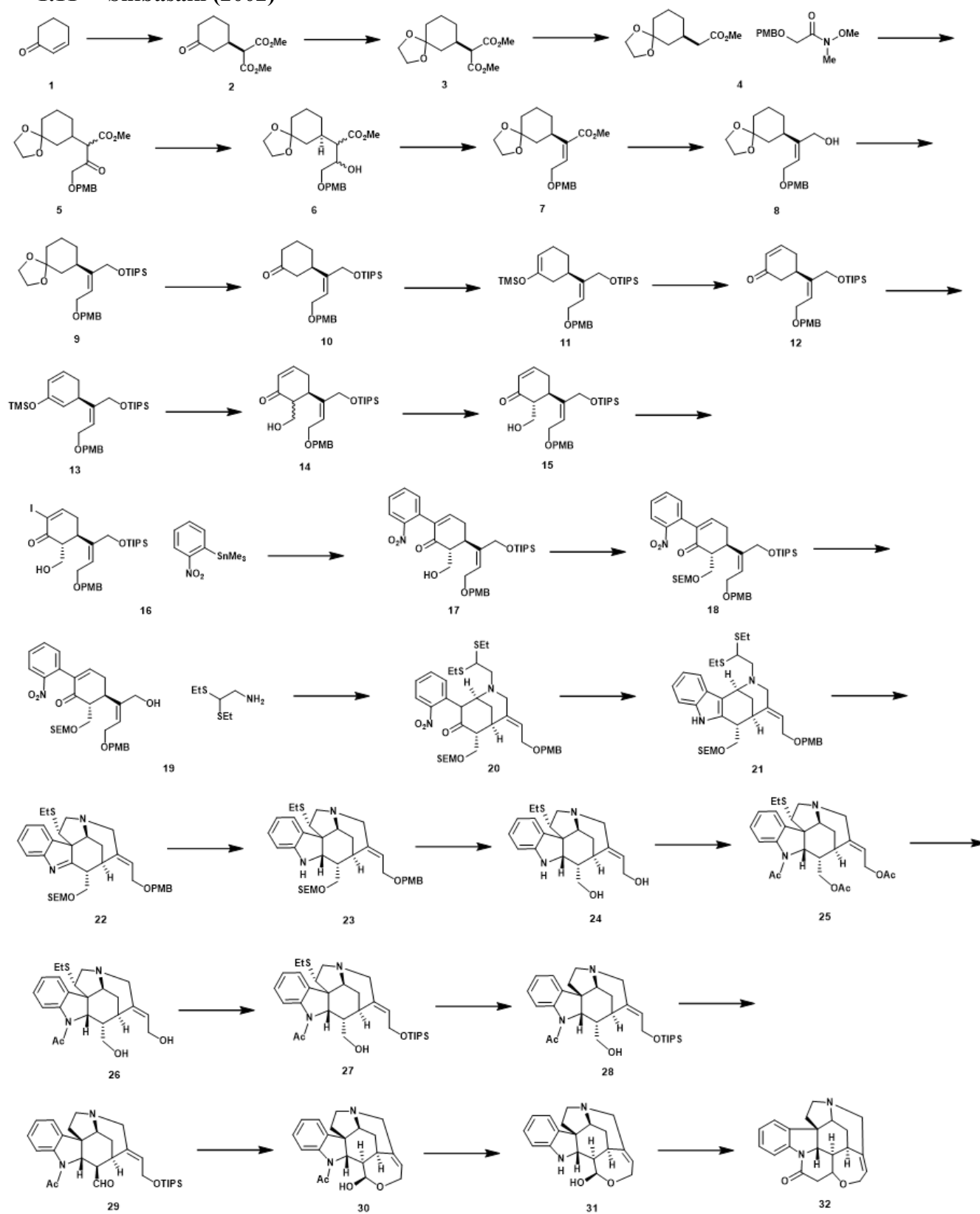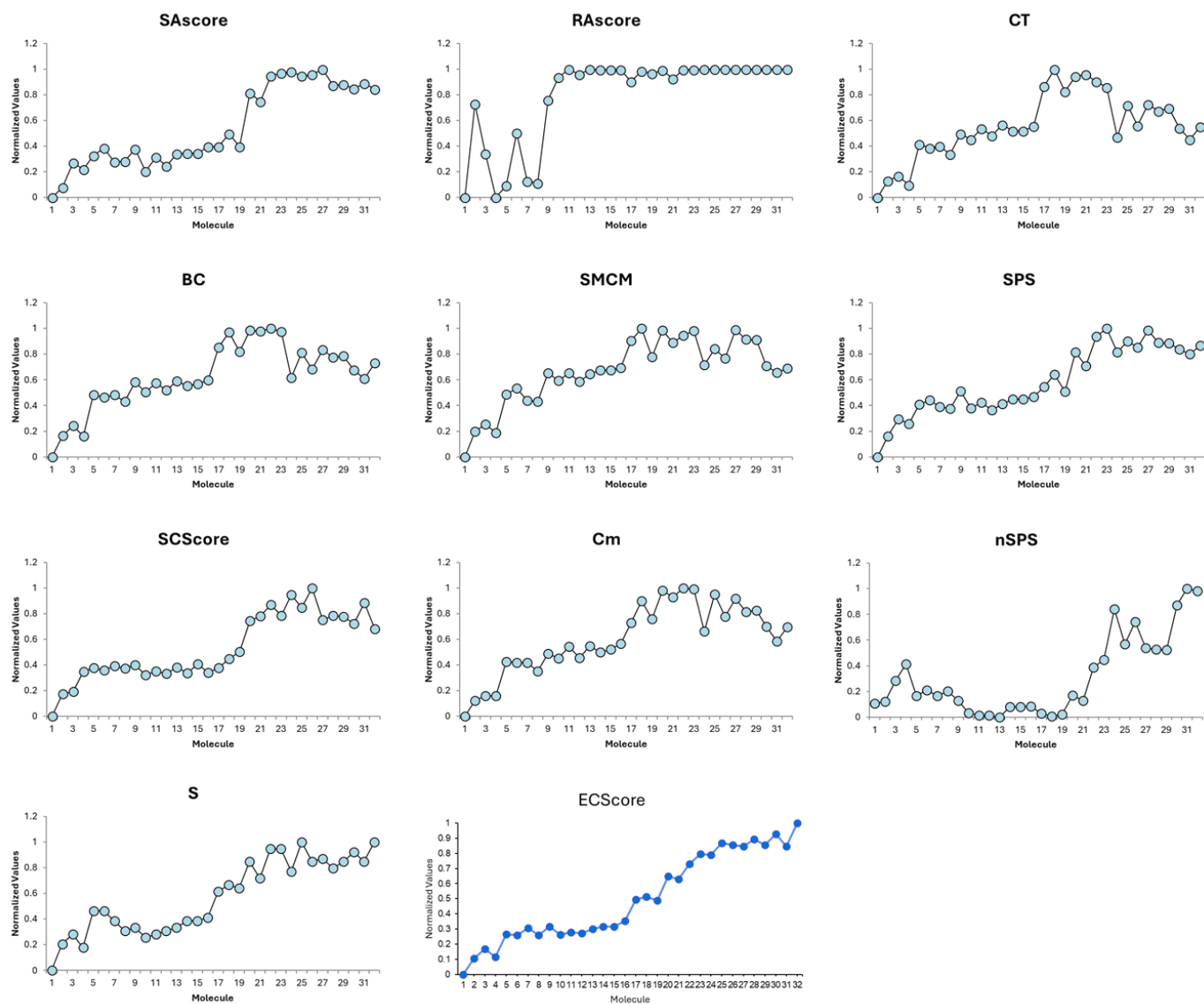
1.15   Reissig (2010)[22]
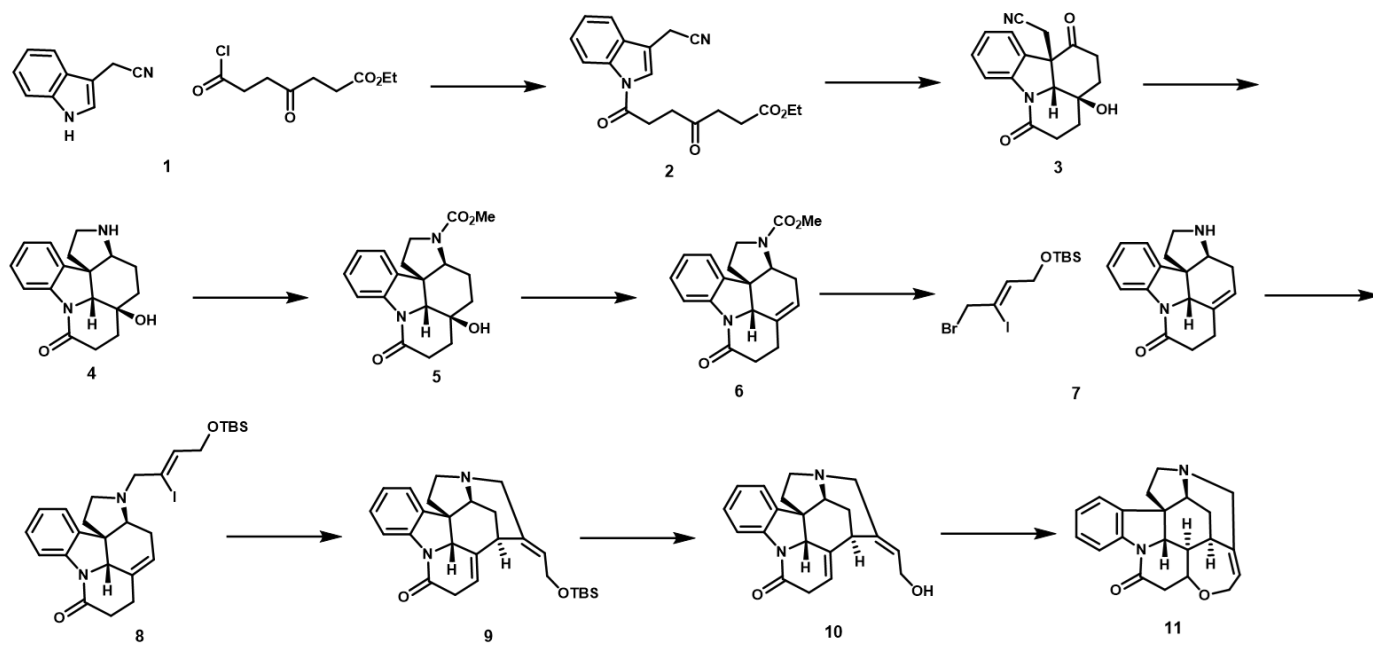
Figure S29. Reissig's 2010 synthesis of Strychnine.
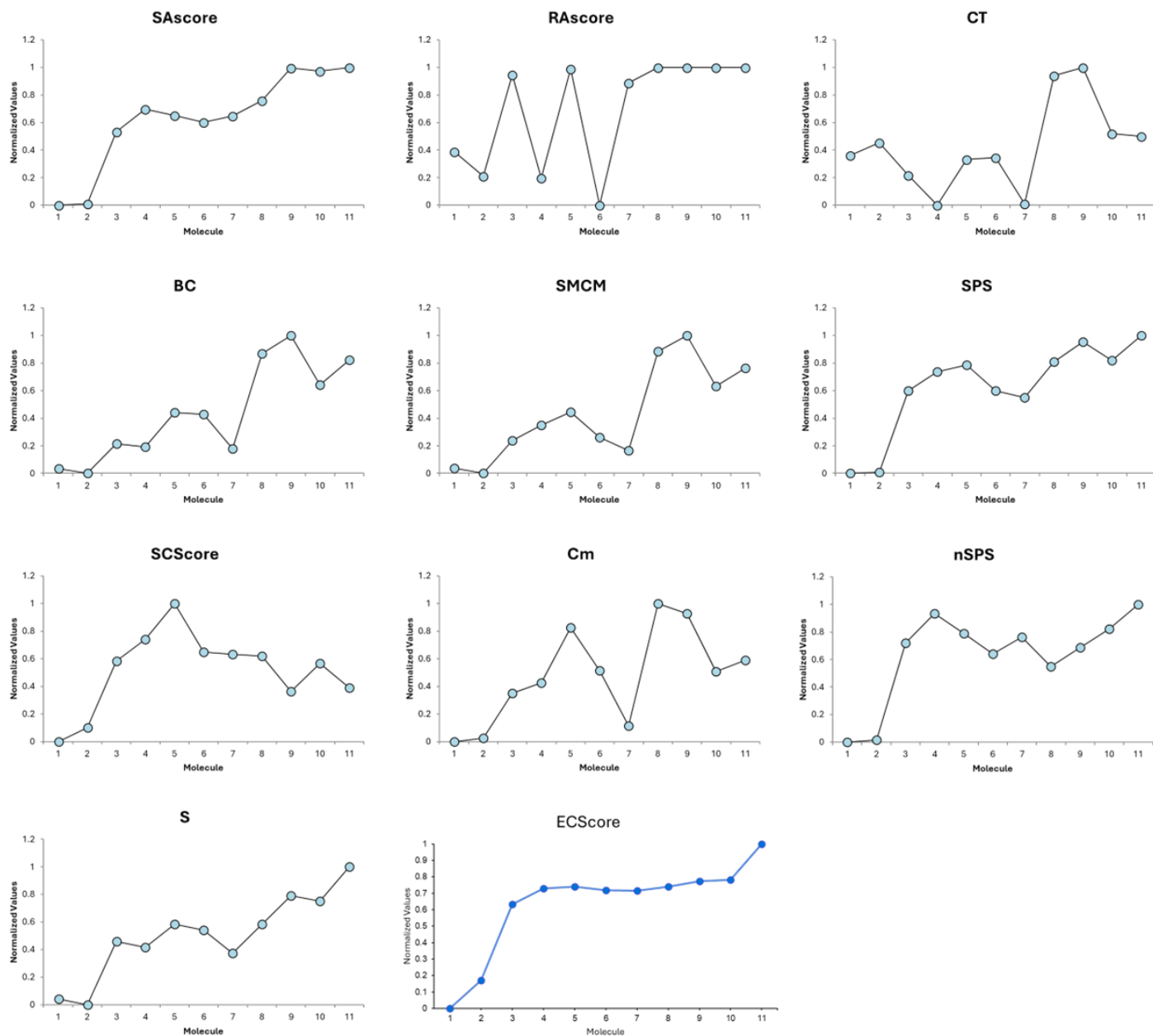
Figure S30. Scoring functions performance on Reissig's 2010 synthesis of Strychnine. Values were normalized between 0 and 1. Scoring function represented in the graph is indicated in the title of the plot.
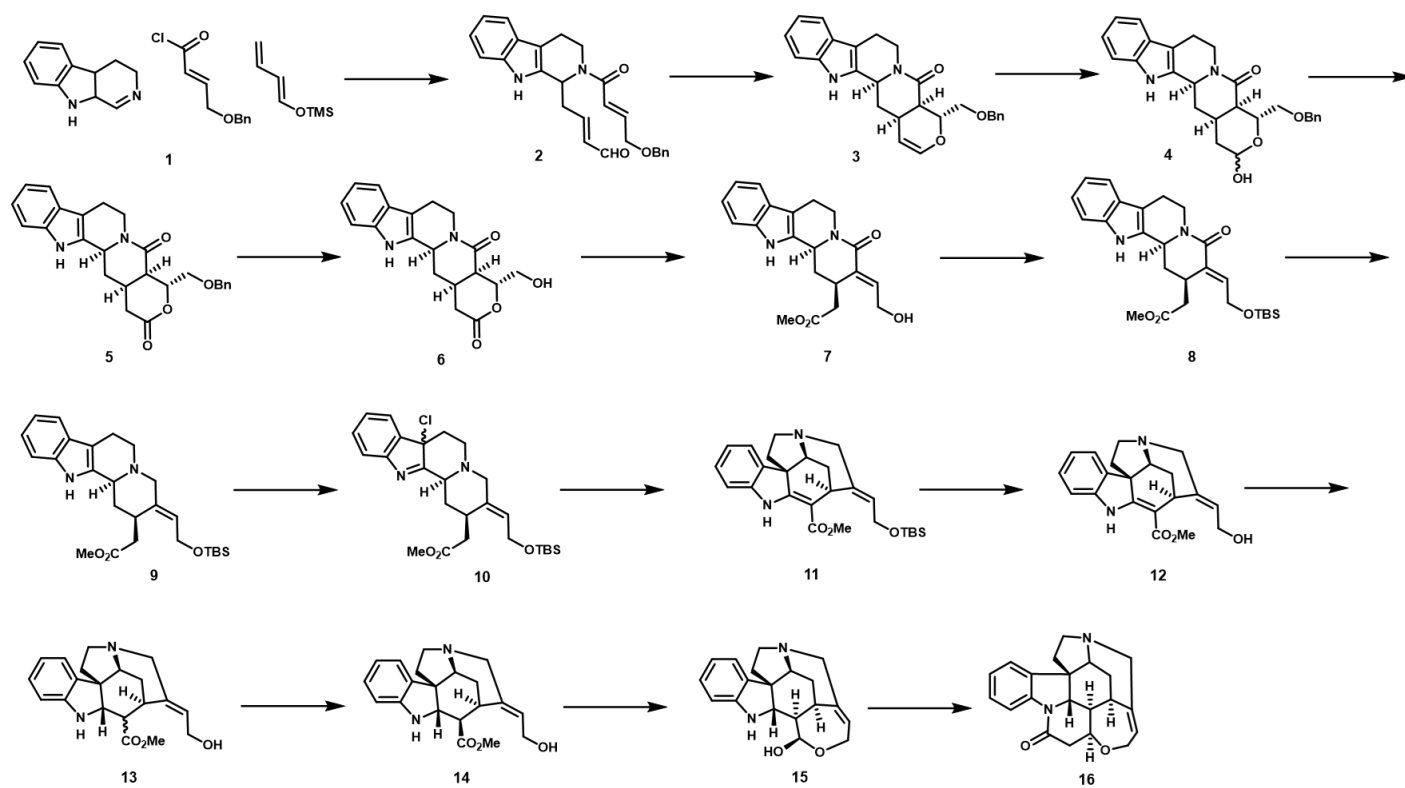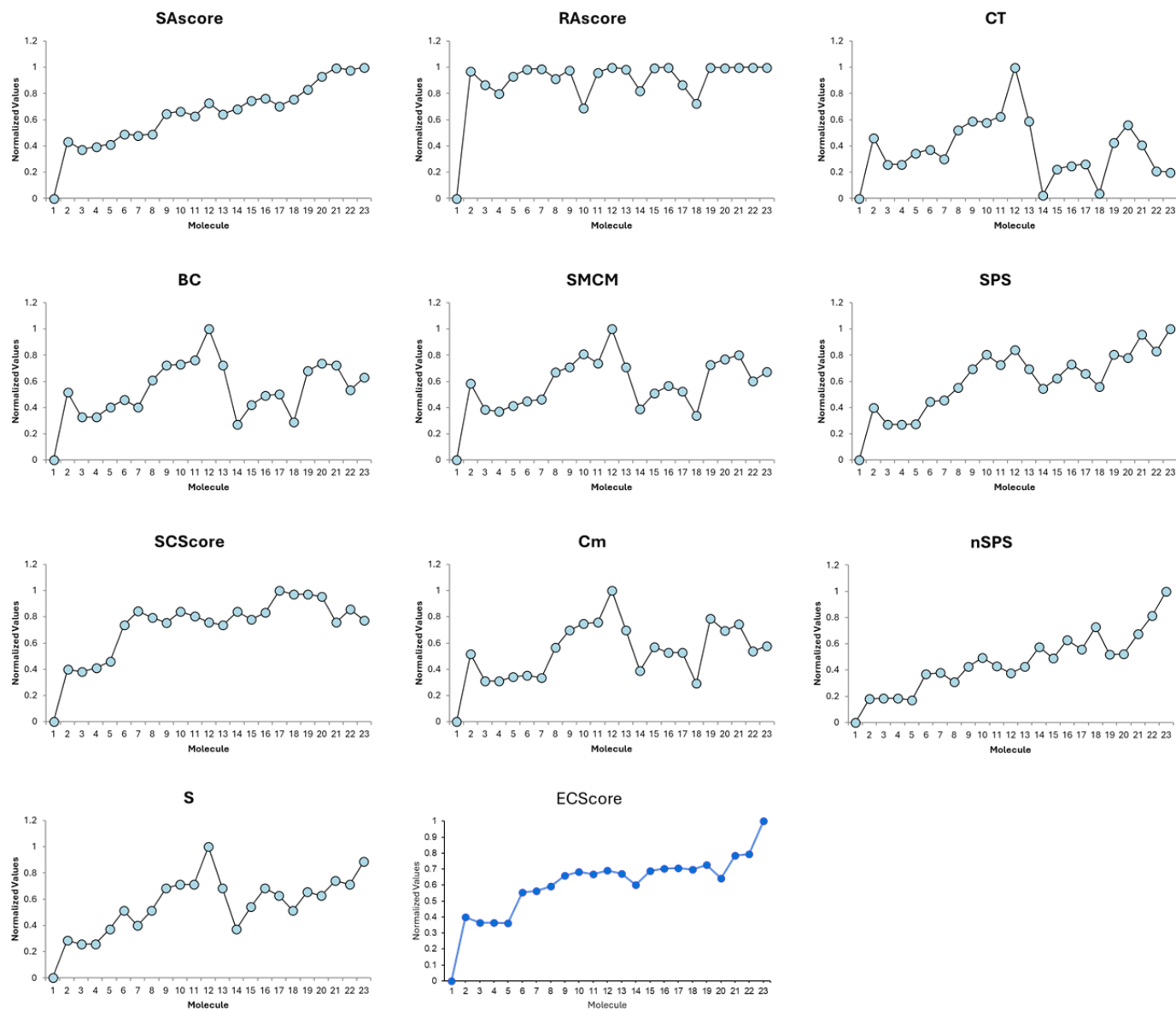
1.16 Andrade (2010)[23, 24]
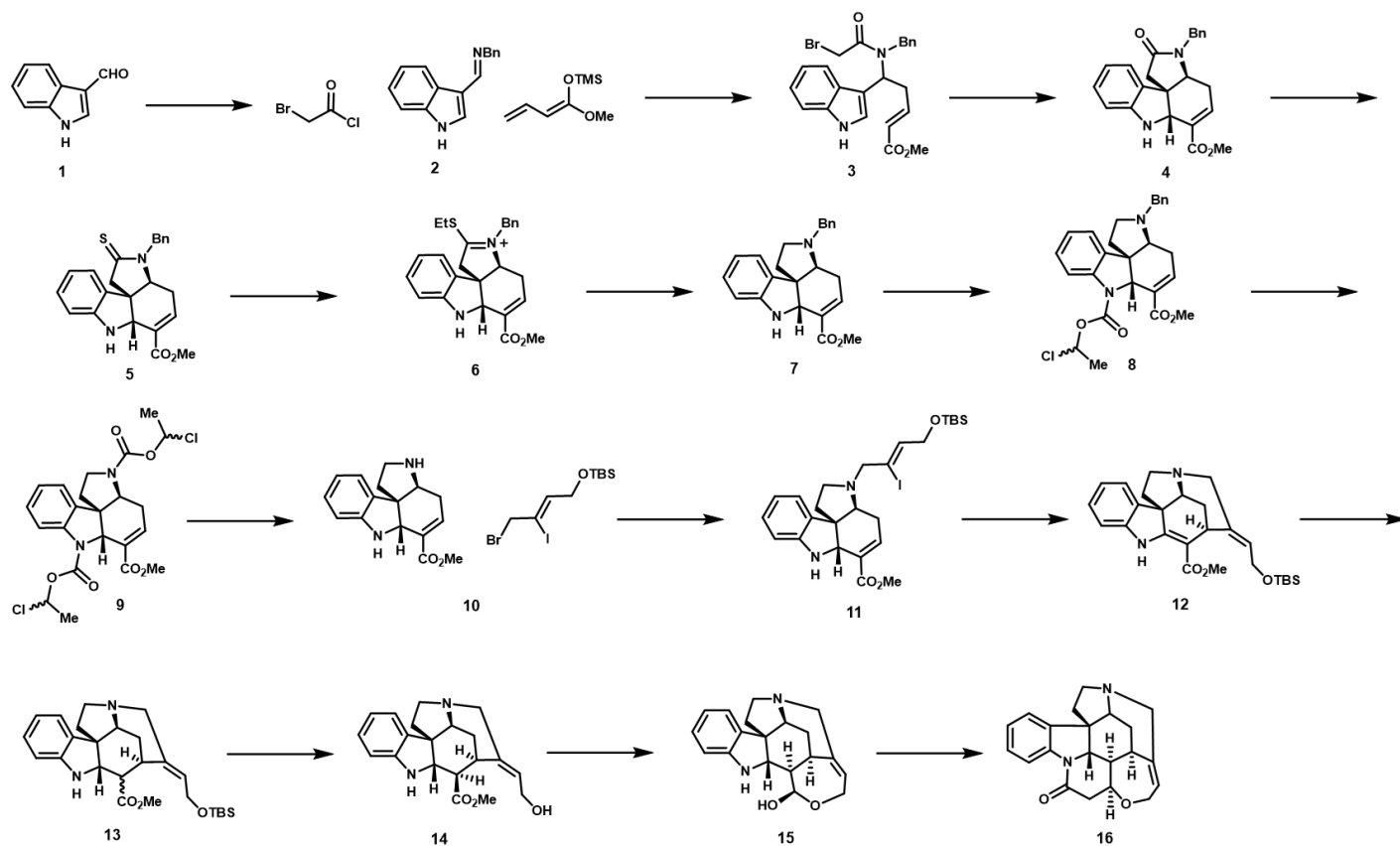
Figure S31. Andrade's 2010 synthesis of Strychnine.
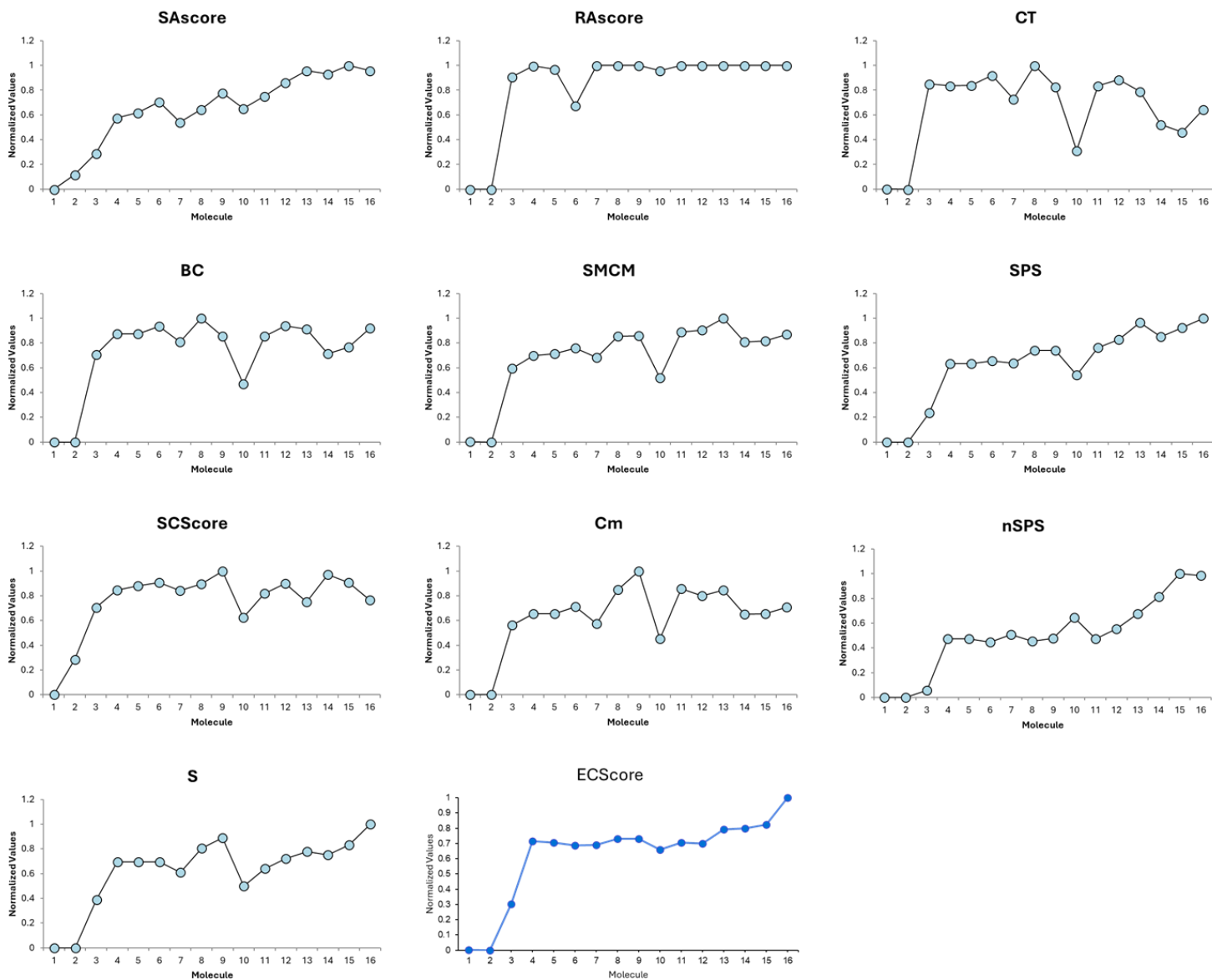
Figure S32. Scoring functions performance on Andrade's 2010 synthesis of Strychnine. Values were normalized between 0 and 1. Scoring function represented in the graph is indicated in the title of the plot.
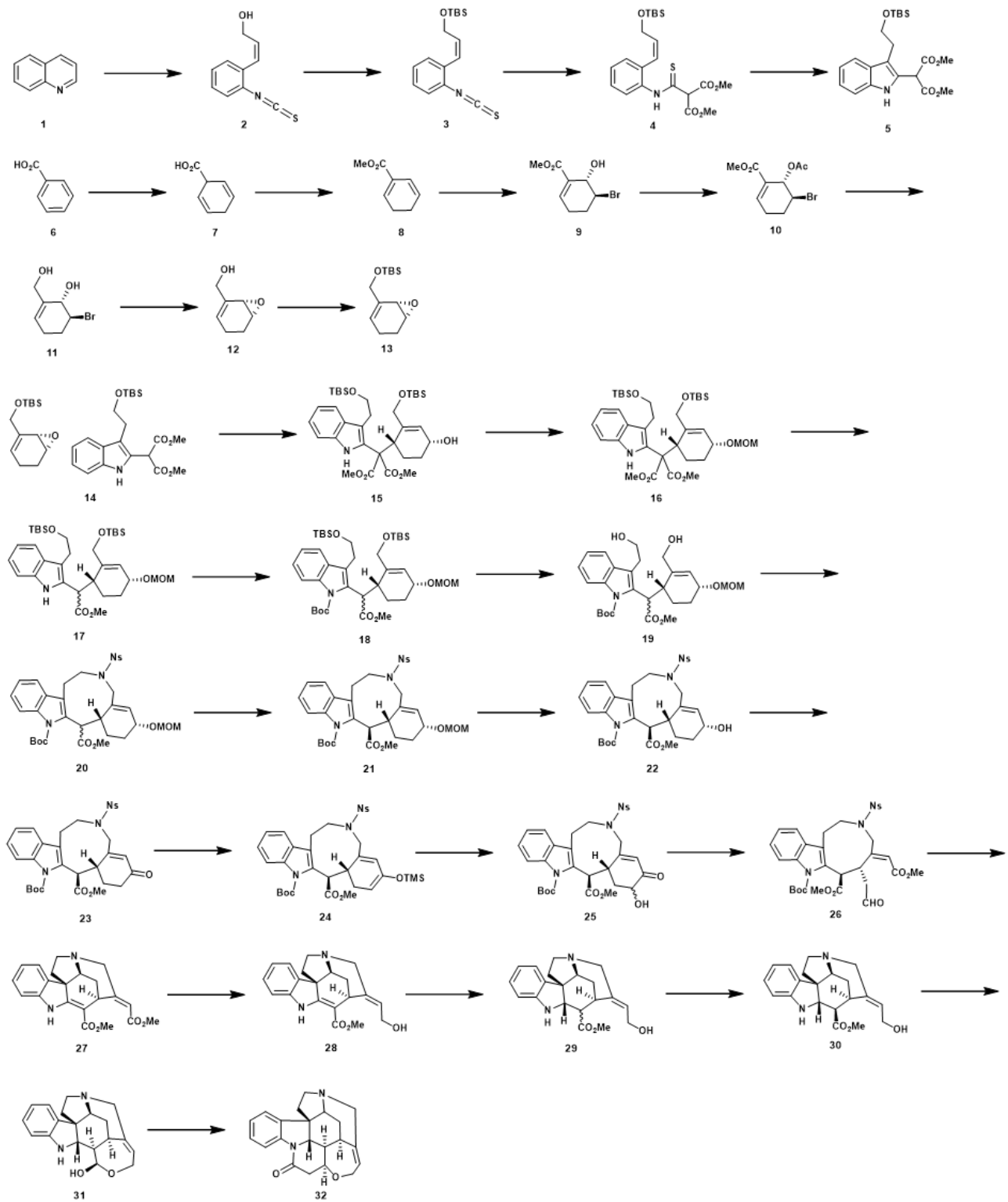
1.17 Vanderwaal (2011)[25]
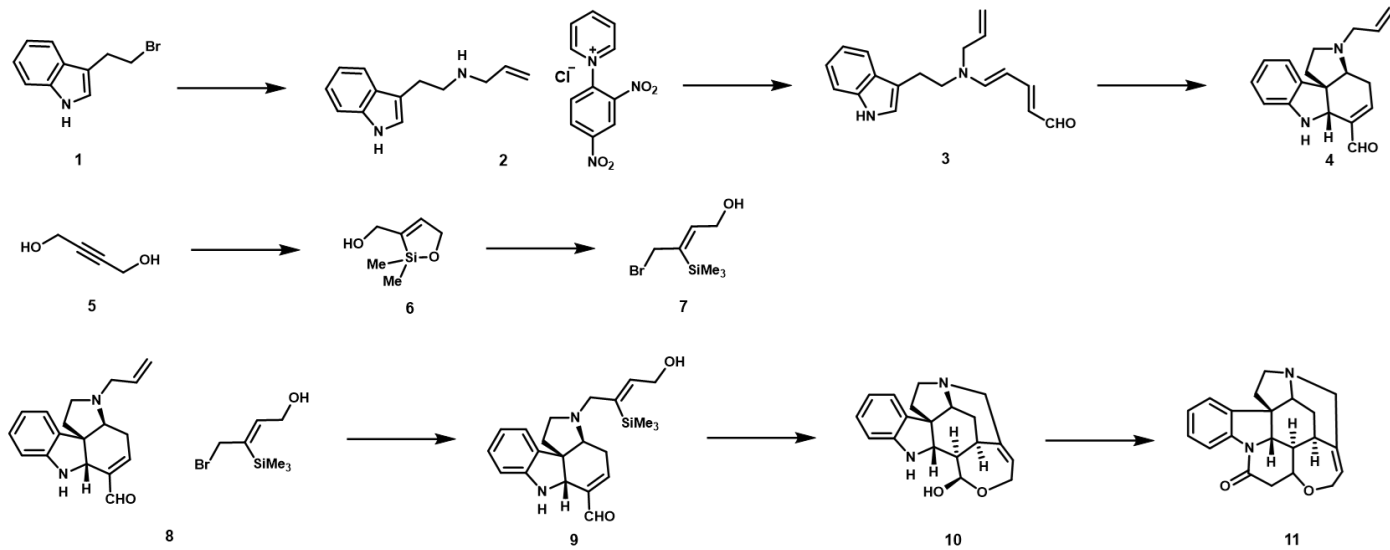
Figure S33. Vanderwaal's 2011 synthesis of Strychnine.

Figure S34. Scoring functions performance on Vanderwaal's 2011 synthesis of Strychnine. Values were normalized between 0 and 1. Scoring function represented in the graph is indicated in the title of the plot.
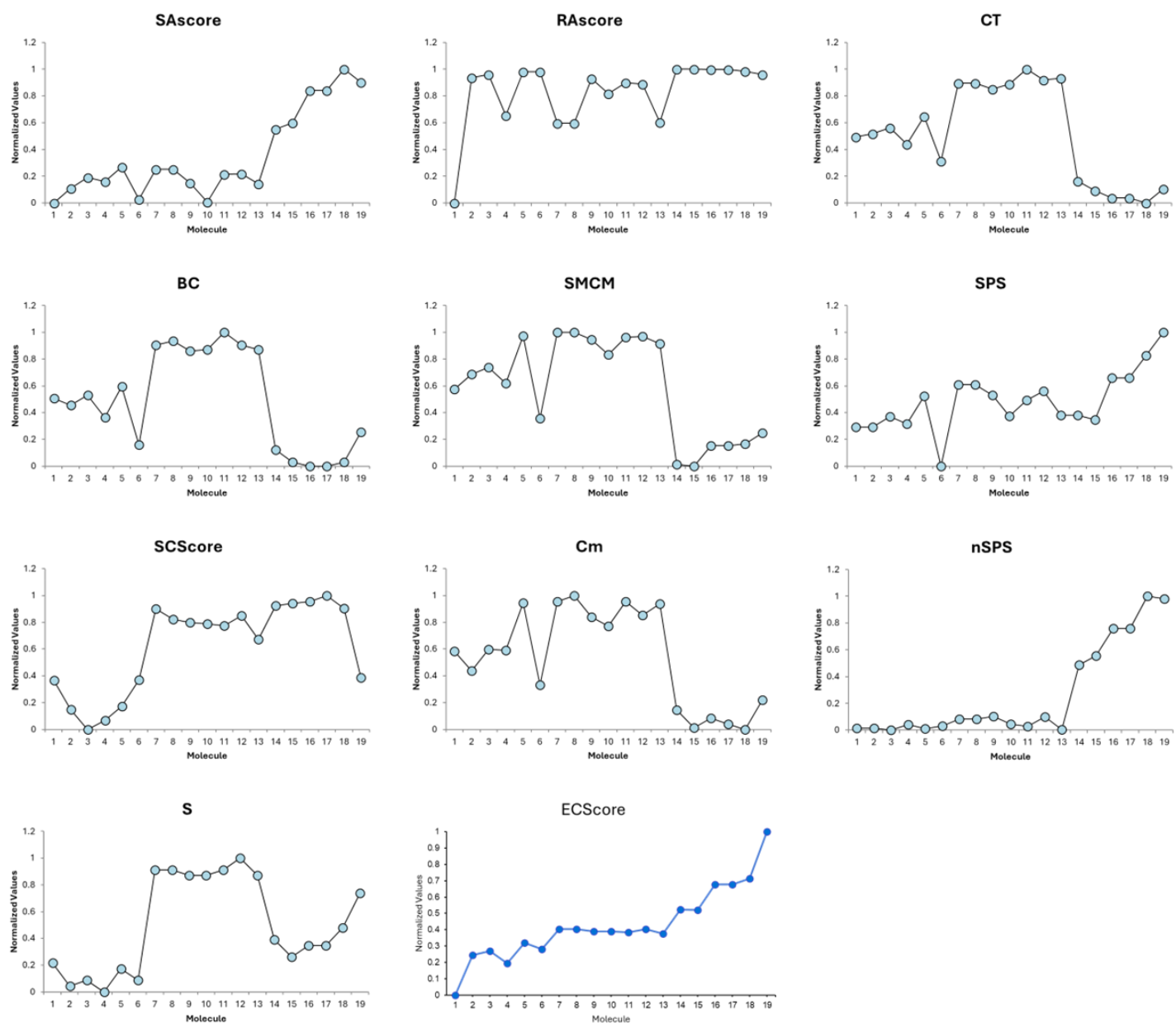
1.18   MacMillan (2011)[26]

Figure S35. MacMillan's 2011 synthesis of Strychnine.

Figure S36. Scoring functions performance on MacMillan's 2011 synthesis of Strychnine. Values were normalized between 0 and 1. Scoring function represented in the graph is indicated in the title of the plot.

3.0 References

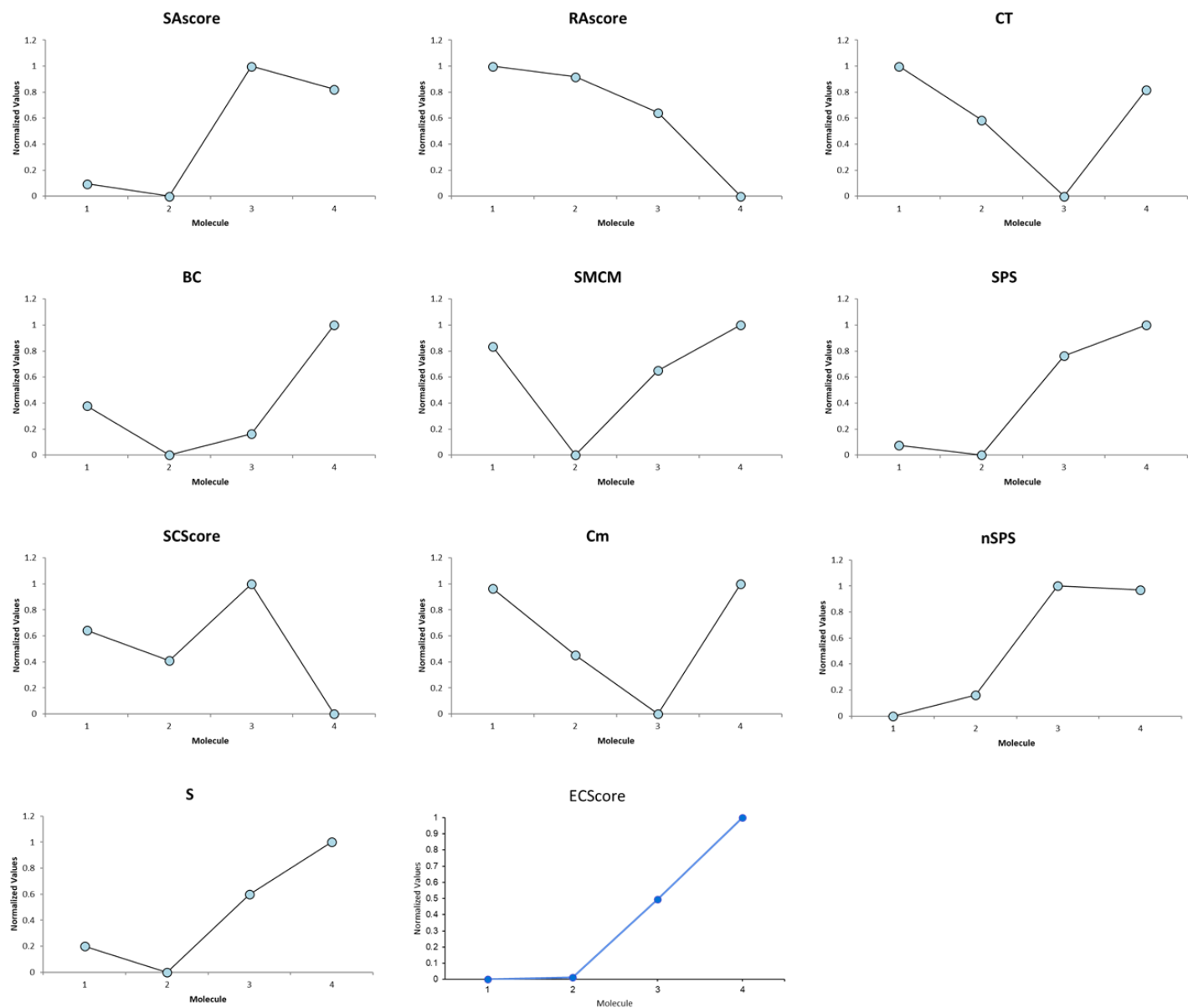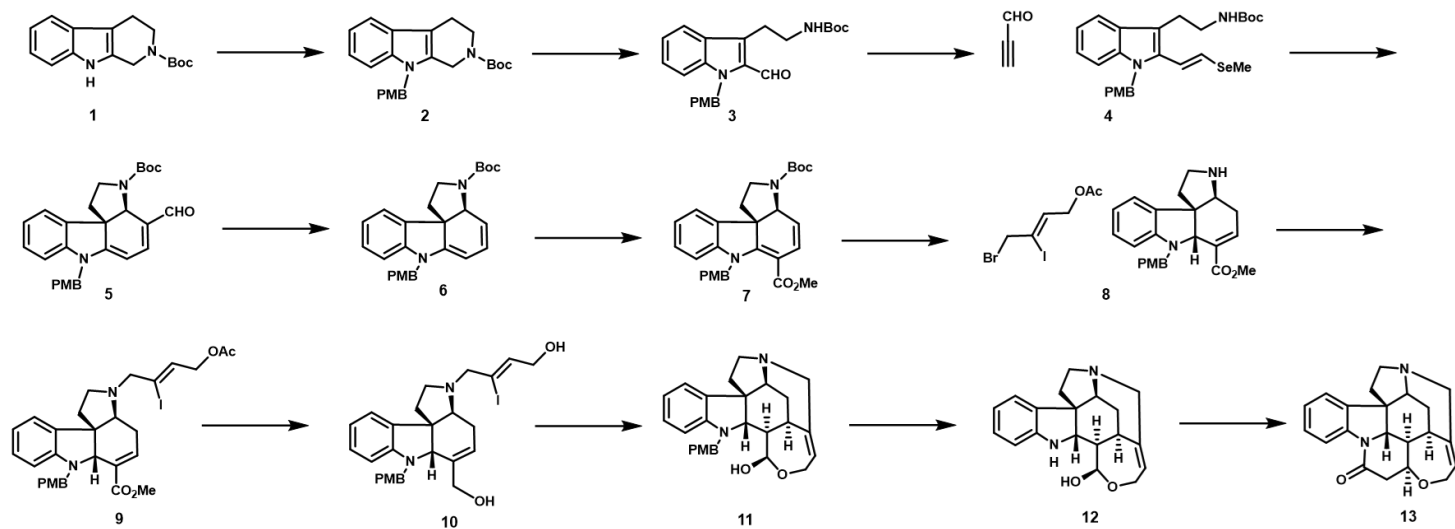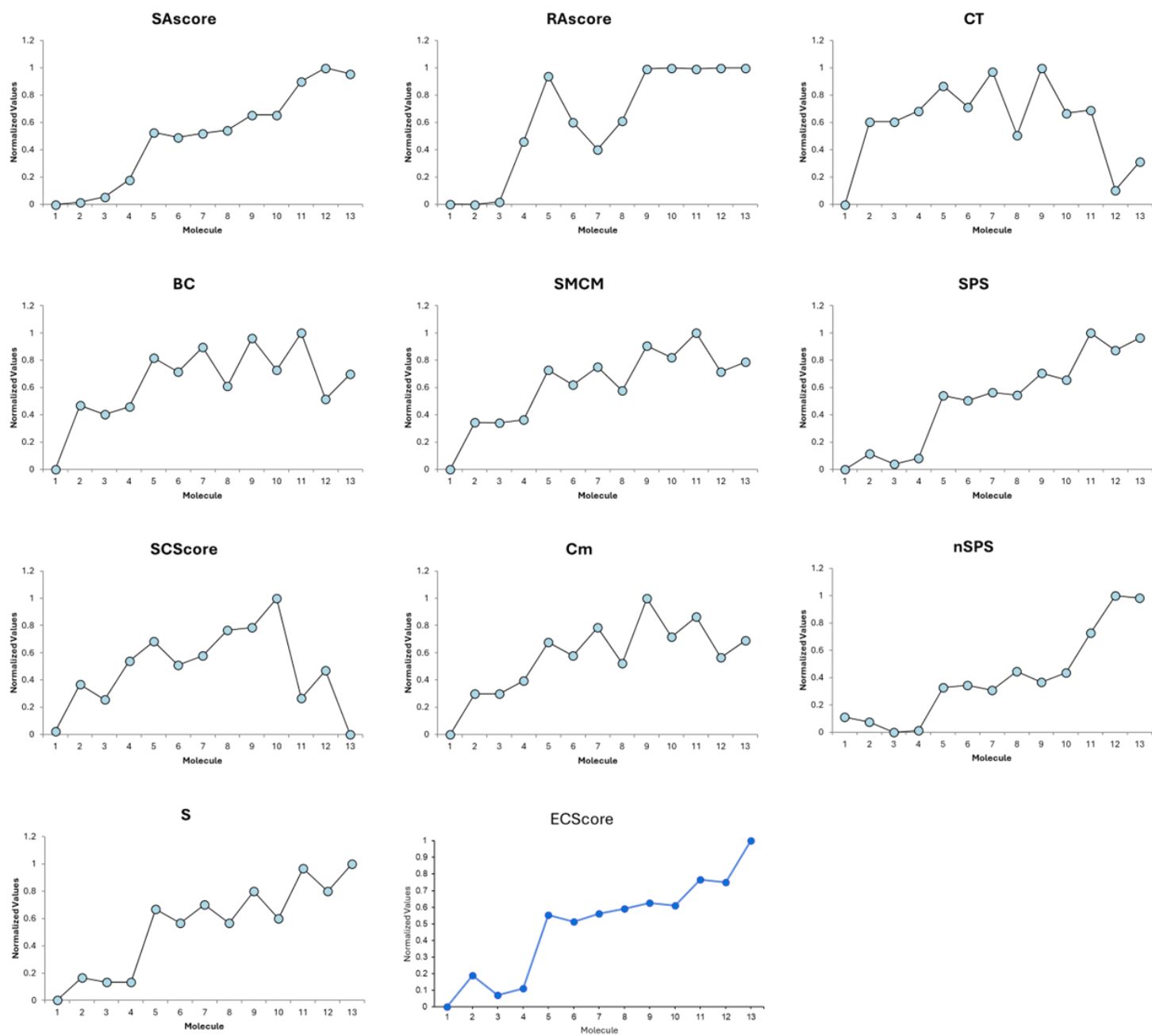(1) Beaudoin, D.; Murphy, P. SynArchive.com The Organic Synthesis Archive. **2011**.

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strychnine using palladium-catalyzed asymmetric allylic substitution. *J. Am. Chem. Soc.* **2003**, *125* (32), 9801-9807.

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