# Rapid conformation searching. Part 2.[1] Similar compounds

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**A strategy for rapidly searching the conformation space of similar compounds is presented. The use of information from previous conformation searches is shown to be effective in the exploration of the conformation space of new systems. This will be useful in exploring the conformation properties of libraries of compounds, or in developing structures from simple model compounds.**

## Introduction

Computational methods are widely used to aid the design and analysis of molecular systems, despite the care that must be taken to assess the accuracy and reliability of computational results and the substantial amount of computer time that is required to perform detailed analyses of molecules which are not large by the present standards of synthetic chemists. The problem of accuracy can be ameliorated by using computational methods to compare similar systems, rather than to determine absolute results. This approach is very commonly used, but necessarily requires that calculations be done on several systems, and so exacerbates the problem of computer time. The preceding paper describes a method for rapidly searching the conformation space of diastereomers.[1] In this paper, we extend the method so that it can be applied to speed the conformation searching of molecules which are similar but not necessarily diastereomeric, nor even isomeric.

Molecules which differ only slightly, such as having an ethyl rather than a methyl group, are likely to have rather similar properties. In particular, their conformation space is likely to be related. A program has been written which will take the output of a conformation search and modify all the conformations by substitution of some of the atoms.† By analogy with our simpler program for creating diastereomers[1] this reduces the time required to perform conformation searches on a series of similar systems.

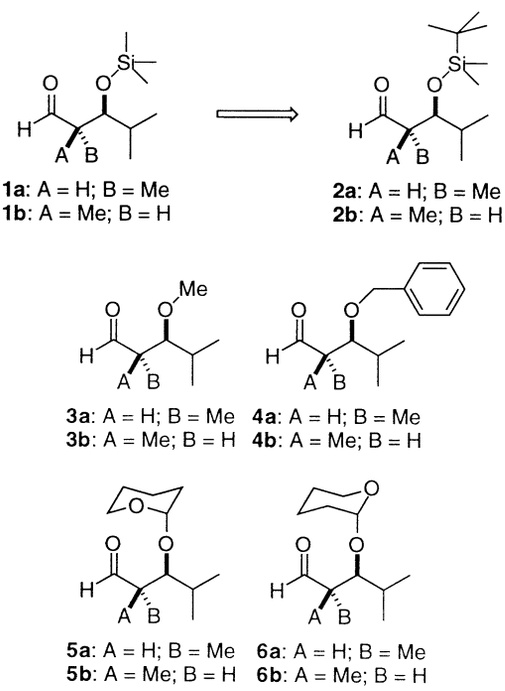



**Fig. 1** TMS transformed to TBDMS and other protecting groups

## Results and discussion

### Example 1

A molecule with a TMS (trimethylsilyl) protecting group is likely to have conformational properties somewhat like the same molecule with a TBDMS (*tert*-butyldimethylsilyl) protecting group. However, the conformation search[2] of the former will be easier by a factor of more than three, because it has fewer rotatable torsion angles and the smaller structure has fewer interactions to calculate. As a result, if an interesting molecule contains a TBDMS group, a conformation search may sometimes be done on the molecule in which the TBDMS is replaced by a TMS group, in order to speed up the process. Unfortunately, this is not always a good approximation.

Molecules **1a** and **1b** (Fig. 1) are simplified forms of **2a** and **2b** which may be modelled in place of the system which was actually used in the experiment.[3] A full conformation search of the TMS-protected molecule **1a** takes *ca.* 2 h on a Silicon Graphics R4400 Indigo, and finds 113 conformations. The corresponding search for TBDMS takes *ca.* 9 h and finds 251 structures. Our new program takes the results of the shorter search, modifies them by turning the TMS group into a TBDMS group, and so produces a conformation search of the more complex system in a shorter time than would otherwise be possible. The results of various exchanges are given in Table 1. Various procedures were possible, which are listed in Table 2. The simplest, Proc A, would simply be to replace a TMS group with a TBDMS group, but this would not take account of the asymmetry of the new group. This can be overcome by trying to decide on the best orientation for the new group (Proc B) or by trying all possible orientations (Proc C).

**Optimised replacement (Proc B).** The program uses a simple estimate of steric effects to calculate the best direction for a bulky new group to point, and so tries to fit the TBDMS group into the best space for it. This is a rapid procedure, but cannot produce more conformations than were found by the TMS search. When applied to **1a**, the replacement and reminimisation took 15 min and found 92 conformations within 50 kJ $mol^{-1}$ of the global minimum. This is more than a third of the number found by the Monte-Carlo search, and it includes the global minimum structure, and 13 of the 14 structures within 4 kJ $mol^{-1}$ of the global minimum. The corresponding procedure with **1b** also found over a third of the Monte-Carlo conformations, including the global minimum and all of the structures within 4 kJ $mol^{-1}$ of the global minimum. The total time for a conformation search of **1a** or **1b**, followed by the conversion

† The executable for the program is available on the Cambridge Chemistry Department World-Wide-Web server (http://www.ch.cam.ac.uk/MMRG/software/).

**Table 1** Conformation searches on compounds **1–6**

| | Time required/ min | Global minimum/ kJ mol$^{-1}$ | Conformations within | | |
|---|---|---|---|---|---|
| | | | 4 kJ mol$^{-1}$ | 10 kJ mol$^{-1}$ | 50 kJ mol$^{-1}$ |
| **2a** Monte-Carlo 3000 steps | 543 | 53.59 | 14 | 55 | 251 |
| **1a** Monte-Carlo 1000 steps | 118 | 44.22 | 14 | 38 | 113 |
| Change **1a** into **2a** Proc B | 15 | 53.59 | 13 | 37 | 92 |
| Change **1a** into **2a** Proc C | 59 | 53.59 | 13 | 47 | 184 |
| **2b** Monte-Carlo 3000 steps | 550 | 49.21 | 2 | 17 | 265 |
| **1b** Monte-Carlo 1000 steps | 113 | 39.94 | 2 | 15 | 117 |
| Change **1b** into **2b** Proc B | 13 | 49.21 | 2 | 14 | 100 |
| Change **1b** into **2b** Proc C | 60 | 49.21 | 2 | 16 | 192 |
| **3a** Monte-Carlo 1000 steps | 48 | 49.93 | 6 | 24 | 99 |
| Change **1a** into **3a** Proc A | 4 | 49.93 | 6 | 21 | 80 |
| **3b** Monte-Carlo 1000 steps | 46 | 50.02 | 4 | 26 | 109 |
| Change **1b** into **3b** Proc A | 5 | 50.02 | 4 | 22 | 79 |
| **4a** Monte-Carlo 2500 steps | 573 | 63.86 | 15 | 67 | 275 |
| Change **3a** into **4a** Proc B | 56 | 63.86 | 14 | 56 | 221 |
| Change **3a** into **4a** Proc D | 118 | 63.86 | 15 | 62 | 249 |
| **4b** Monte-Carlo 2500 steps | 518 | 62.88 | 5 | 45 | 293 |
| Change **3b** into **4b** Proc B | 62 | 62.88 | 5 | 43 | 246 |
| Change **3b** into **4b** Proc D | 128 | 62.88 | 5 | 45 | 272 |
| **5a** Monte-Carlo 1000 steps | 140 | 9.08 | 8 | 27 | 269 |
| Change **3a** into **5a** Proc E | 25 | 9.08 | 7 | 18 | 93 |
| Change **3a** into **5a** Proc F | 77 | 9.08 | 8 | 26 | 126 |
| **5b** Monte-Carlo 1000 steps | 123 | 7.34 | 2 | 17 | 133 |
| Change **3b** into **5b** Proc E | 27 | 7.33 | 2 | 16 | 87 |
| Change **3b** into **5b** Proc F | 81 | 7.33 | 2 | 17 | 133 |
| **6a** Monte-Carlo 1000 steps | 130 | 8.64 | 3 | 21 | 150 |
| Change **3a** into **6a** Proc E | 26 | 8.64 | 3 | 18 | 92 |
| Change **3a** into **6a** Proc F | 74 | 8.64 | 3 | 20 | 143 |
| **6b** Monte-Carlo 1000 steps | 124 | 7.75 | 3 | 13 | 159 |
| Change **3b** into **6b** Proc E | 28 | 7.74 | 3 | 12 | 102 |
| Change **3b** into **6b** Proc F | 83 | 7.74 | 3 | 14 | 152 |

**Table 2** The procedures for converting groups

| Procedure | Description | Example | Difficulty[a] |
|---|---|---|---|
| A | Conversion of groups with the same symmetry | TMS ⇒ Me | 1 |
| B | Conversion of a more symmetrical to a less symmetrical group, with the orientation decided by a simple optimisation routine | TMS ⇒ TBDMS<br>Me ⇒ Bn | 1 |
| C | Conversion of a more symmetrical to a less symmetrical group, including three possibilities for the orientation of the new group by rotating around the bond that is broken and reformed | TMS ⇒ TBDMS<br>Me ⇒ Bn | 3 |
| D | As Proc C, but also including rotation around a bond within the group being added | Me ⇒ Bn | 6 |
| E | As Proc C, but omitting orientations which are likely to be high in energy | Me ⇒ THP | 2 |
| F | As Proc E, but also twisting around an adjacent bond | Me ⇒ THP | 6 |

[a] The number of new conformations divided by the number of old conformations.

and reminimisation was less than 135 min, compared with the 9 h required for the search of **2a** and **2b**. The converted structures were reminimised rather more quickly than the Monte-Carlo structures, because they tended to be close to minima on the potential energy surface.

**Exhaustive replacement (Proc C).** It is clear that the conformation space of **2a** and **2b** is likely to be larger than that of **1a** and **1b**, and so it is desirable to have a method of converting the TMS group into the TBDMS group which is not limited to the number of structures from the smaller search. This can be achieved by minimising several different conformations of the TBDMS structure, with rotating around the O–Si bond so that the *tert*-butyl group points in different directions. It was decided to rotate the group in 120° increments, creating (before minimisation) three times as many conformations as the TMS molecule. This procedure can find up to three times as many structures for **2a** and **2b** as for **1a** and **1b**, although the reminimisation of the new structures will take rather longer than is needed for the optimised replacement strategy. In this case, it took an hour rather than a quarter of an hour, but more than two thirds of the structures from the Monte-Carlo searches of **2a** and **2b** were found, in a third of the total time.

These results gave confidence that these procedures could be used to search the conformation spaces of similar molecules, by mutating one into another. A conformation search of a TBDMS protected compound may only take 50% more time than a TMS protected compound (exhaustive replacement), instead of more than four times as long (full conformation search).

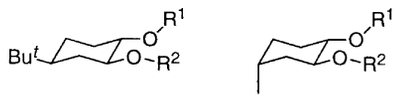
Table 1 records the results of swapping other protecting groups in the same system. Trimethylsilyl to methyl (**1** into **3**) is a small change, as the methyl group adopts the orientation of the trimethylsilyl (Proc A). There was no need to do an exhaustive replacement in this case, and the results were very good. Both *anti* (**3a**) and *syn* (**3b**) diastereomers required only a tenth the time for a Monte-Carlo search, and found 80 and 70% of the structures, respectively, including everything within 4 kJ mol$^{-1}$ of the global minima.

The benzyl group was investigated by mutating the methyl group (**3** into **4**). First, an exhaustive swap (Proc C) was carried out. This was effective, but one structure within 4 kJ mol$^{-1}$ of the global minimum was missing from the resulting file. In order to try and find all the conformations, each conformation of **3a** and **3b** was turned into six new conformations of **4a** and **4b** (Proc D). Three conformations were obtained by replacing each hydrogen of the methyl in turn with a phenyl group. Two conformations were generated from each of these structures by rotating 90° around the new C–C bond. Because phenyl rings are symmetrical, there was no need to rotate by 180° and 270° as well. The time saving in this case for the conversion procedure rather than a new Monte-Carlo search is only a factor of four, but nearly all of the conformations of the benzyl protected molecules were found (>90% in both cases).

Finally, the methyl group was turned into a THP (tetrahydropyran-2-yl) group (**4** converted into **5** and **6**). It is likely that the procedure will work most effectively when the changes made to the molecules are small. This is the largest change that was investigated, and so likely to be the least successful. Only chair conformations of the THP group were considered, and the two diastereomeric forms were considered separately (**5** and **6**). Two conformations of the THP group were generated from each of the conformations of **4**, by rotating around the axial C–O bond, to the two staggered positions which do not eclipse the pyran ring (Proc E). The searches were all fast and found the global minima in all cases. However, the total number of structures found was considerably lower than those found by the full conformation searches. This may be because the THP group is a very different shape from the methyl group. In an attempt to find more structures, six conformations of the THP protected compound were now generated from each conformation of **3**, by twisting around the axial C–O as before, and also around the adjacent O–C bond, in steps of 120° (Proc F ). As should be expected, the searches took three times as long and found rather more structures. The time saving over a full Monte-Carlo search fell to less than 50%. It would seem that Me to THP is too large a change in structure for this procedure to be at its most effective.

**Example 2**

Benzyl groups are very important protecting groups, and their conformational preferences may be affected by π-stacking and other weak non-bonded interactions. We therefore undertook a more detailed study of the replacement of methyl groups by benzyl groups, in order to discover if this group caused particular problems. The transformation of **3** into **4** had gone smoothly. However, if there are two adjacent benzyl groups, or a benzyl group adjacent to some other aromatic group, difficulties might arise. We therefore investigated structures **7** and **8** (Table 3).



**7a**: $R^1$ = Me; $R^2$ = Me **8a**: $R^1$ = Me; $R^2$ = Me
**7b**: $R^1$ = Bn; $R^2$ = Me **8b**: $R^1$ = Bn; $R^2$ = Me
**7c**: $R^1$ = Me; $R^2$ = Bn **8c**: $R^1$ = Me; $R^2$ = Bn
**7d**: $R^1$ = Bn; $R^2$ = Bn **8d**: $R^1$ = Bn; $R^2$ = Bn

Proc B and D were applied in turn to **7a** and **8a**. Both proved to be very effective, the latter requiring about four times longer than the former. We also tried changing one benzyl group, minimising, and then changing the other benzyl group. This gave a result intermediate in terms of time and the number of structures found. These results suggest that changing methyl groups into benzyl groups is not a particular problem.

**Example 3**

Macrocyclic stereocontrol has been used in a variety of syntheses to good effect. For example, all of the double bonds in molecule **9a** (Fig. 2, an intermediate in Still and Romeros' polyepoxide route towards polyether antibiotics[4]) can be epoxidised stereoselectively to form **10a** (the *ddd* isomer, Table 4). However, it would be useful to be able to make **10b** (*ddu*), because this would be a useful intermediate in a synthesis of monensin. Is it possible to design a molecule which would do this? A wide variety of similar molecules could be envisaged, but a conformation search on each would take a prohibitively

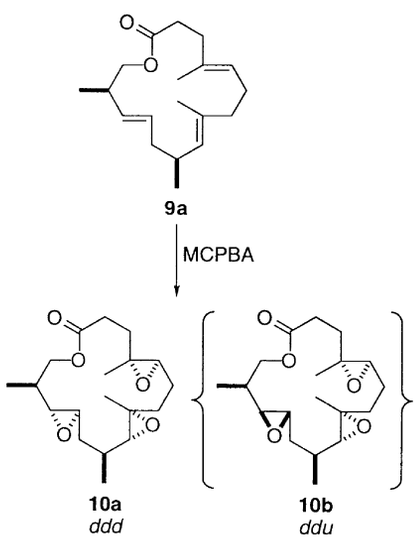



**Fig. 2** Macrocyclic stereocontrol

**Table 3** Multiple benzyl groups

| | Time required/ min | Global minimum/ kJ mol$^{-1}$ | Conformations within 4 kJ mol$^{-1}$ | 10 kJ mol$^{-1}$ | 50 kJ mol$^{-1}$ |
|---|---|---|---|---|---|
| **7a** Systematic search[a,b] | 8 | 85.05 | 6 | 8 | 11 |
| **7d** Monte-Carlo 1000 steps[b] | 1766 | 106.1 | 11 | 38 | 107 |
| Change **7a** into **7d** Proc B | 165 | 106.1 | 10 | 27 | 71 |
| Change **7a** into **7d** Proc D | 627 | 106.1 | 10 | 36 | 93 |
| Change **7a**–**7b**–**7d** Proc D | 292 | 106.1 | 9 | 27 | 77 |
| Change **7a**–**7c**–**7d** Proc D | 306 | 106.1 | 8 | 26 | 79 |
| **8a** Monte-Carlo 2500 steps | 457 | 63.82 | 9 | 11 | 57 |
| **8d** Monte-Carlo 2500 steps | 3749 | 86.41 | 12 | 46 | 559 |
| Change **8d** into **8a** Proc B | 673 | 86.41 | 12 | 35 | 400 |
| Change **8a** into **8d** Proc D | 2691 | 86.41 | 12 | 45 | 472 |
| Change **8a**–**8b**–**8d** Proc D | 1376 | 86.41 | 12 | 39 | 438 |
| Change **8a**–**8c**–**8d** Proc D | 1423 | 86.41 | 12 | 39 | 447 |

[a] A systematic search was used rather than Monte-Carlo, because this is more efficient for molecules with very limited degrees of freedom. [b] Only chair conformations were considered.

**Table 4** Searching for macrocyclic stereocontrol

| | Time required/ min | Conformations within 4 kJ mol$^{-1}$ | Conformations within 50 kJ mol$^{-1}$ | Predicted pattern of epoxidation[a] |
|---|---|---|---|---|
| Monte-Carlo **9a** (5000 steps) | 1301 | 4 | 1312 | *ddd*[b] |
| Monte-Carlo **9b** (5000 steps) | 1341 | 11 | 1234 | *uuu* |
| **11** Proc A | 256 | 5 | 1125 | *duu* |
| **12** Proc A | 250 | 8 | 1112 | *ddd* |
| **13** Proc A | 441 | 1 | 695 | *ddd* |
| **14** Proc A | 442 | 5 | 797 | *ddd* |
| **15** Proc A | 300 | 3 | 1037 | *udu* |
| **16** Proc A | 145 | 4 | 760 | *ddd* |
| **17** Proc A | 154 | 4 | 766 | *ddd* |
| **18** Proc A | 279 | 14 | 624 | *ddd* |
| **19** Proc A | 265 | 5 | 613 | *ddu* |
| **20** Proc A | 175 | 5 | 717 | *ddd* |
| Monte-Carlo **19** (5000 steps) | 1803 | 7 | 1140 | *ddu* |

[a] The stereochemistry is up *u* or down *d* as shown, going clockwise around the ring from the lactone. [b] This correlates with experiment.[4]

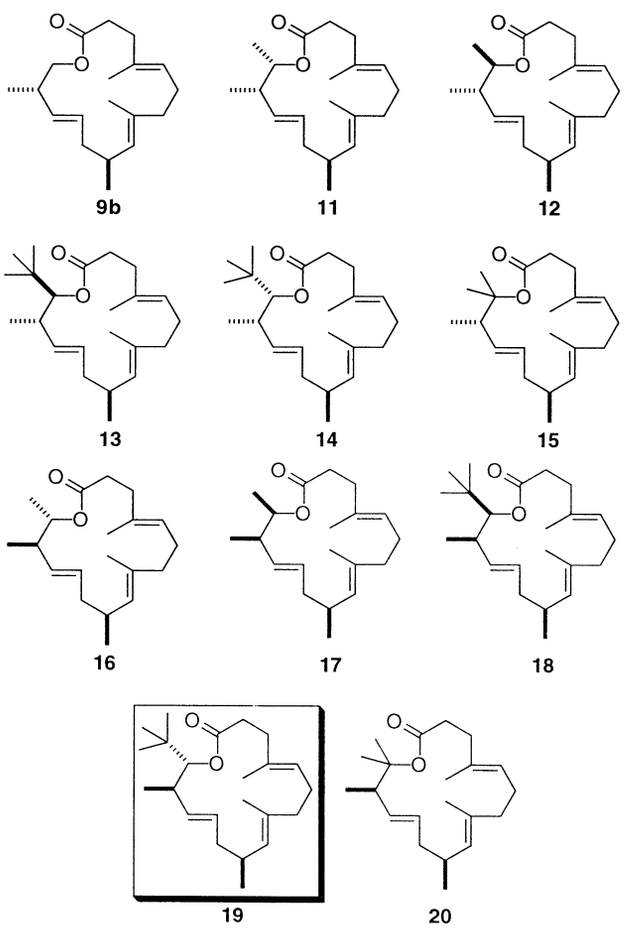



**Fig. 3** Alternative macrocycles

long time. Our new program allows new molecules to be tested rapidly. Results of a conformation search of **9a** and **9b** were available,[1] and these were used as the basis for the new searches. The molecules **11–20** (Fig. 3) were considered, and the results of conformation searches (Proc A) are given in Table 4. It was possible to search the conformation space of all the ten new structures in about the same time as was required for the two conformation searches of the parent structures **9a** and **9b**.

The results suggest that **19** should have the correct geometry, and so a complete conformation search was undertaken on this structure, to test the result. This conformation search, which took nearly seven times longer than the first conformation analysis of **19**, found the same global minimum and the same two lowest energy local minima. This confirmed the result, that the global minimum structure would be likely to give the product with the desired stereochemistry (**10b**). Unfortunately, there are several low energy local minima with contrasting conformational preferences, so the selectivity would not be high.

## Conclusions

A program has been developed that will take the result of a conformation search and substitute particular atoms. This is useful in the conformation searches of similar molecules. The program has been tested by varying the protecting group of alcohols, and by considering a series of potential intermediates in a synthesis using macrocyclic stereocontrol. This has demonstrated that it is feasible to examine the conformation space of a single compound protected in different ways without needing to perform a full conformation space on each one. In addition, as a molecule is built up from simpler precursors, it is possible to build up the conformation analysis at the same time. A model compound can lead to the analysis of the full compound, in considerably less time.

## Acknowledgements

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