

Superstructure Searching Algorithm for Generic Reaction Retrieval

Qian Zhu,^{†,‡} Jianhua Yao,^{*,†} Shengang Yuan,[†] Feng Li,[†] Haifeng Chen,[†] Wei Cai,^{†,‡} and Quan Liao^{†,‡}

Laboratory of Computer Chemistry and Chemoinformatics and Graduate School of the Chinese Academy of Sciences, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354, Fenglin Road, Shanghai 200032, China

Received December 2, 2004

Chemical reaction knowledge is usually summarized and retrieved by chemists from references, journals, and reaction databases. To rigorously extract chemical reaction knowledge from large data sets, computer algorithms become much more important. This paper presents a new approach, superstructure searching (SSS) algorithm, for generic reaction retrieval. The algorithm considers all known reaction patterns from the targeted structure and assigns synthetic routes for new chemical compounds. This algorithm consists of screening, atom-by-atom comparison, and computation of R-groups' similarity.

1. INTRODUCTION

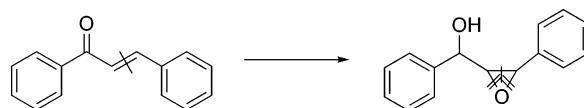
Chemical reaction knowledge is usually summarized and retrieved by chemists from references, journals, and reaction databases. At present, the main methods used to derive chemical reaction knowledge are structure/substructure search and similarity search algorithms, which are implemented in commercial chemical reaction databases, such as the Beilstein CrossFire Database¹ (MDL product). These algorithms assume the size of a target structure (query structure) is smaller than structures in the database. However, chemists are interested in making novel compounds, which the structure size can be greater than the ones in the database. To find a synthetic route to make a novel compound, the superstructure search (SSS) algorithm is described in this paper. The SSS is successfully applied to identify generic reaction knowledge in our lab. In the 1980s, Wipke² initially reported the superstructure search algorithm for computer-aided synthetic planning. But he applied the algorithm just for assisting in finding possible starting materials of the target molecule, not for synthesis design.²

In this paper, we present a method for deriving generic reaction knowledge based on the SSS, which assists in synthesis design. It is combined reasonably by the generic reaction knowledge base and the SSS.

2. GENERIC REACTION KNOWLEDGE BASE

Generic reactions induced from known reaction information are represented by chemical schemes including the information of similar compounds reacting under similar conditions. The generic reaction knowledge base consists of generic reactions. Two papers for inducing generic reactions from huge amounts of reaction information in MDL reaction database¹ were published.^{3,4} Although the concepts used in the works of ref 3 are the same as that of ref 4, their definitions and strategies are different.

Scheme 1. An Example of a Specific Reaction⁵



The generic reaction model consists of three layers (see Figure 1): specific reaction, reaction core, and reaction type, which is defined in the works in ref 4. The definitions for "reaction type" and "reaction cores" are more reasonable than that in ref 3.

2.1. Specific Reactions. Individual reactions in MDL reaction databases are organic reactions with reaction centers (bonds built, broken, or changed), shown in Scheme 1.

2.2. Reaction Types. Reaction types are reaction schemes with reaction centers and their environment, R-groups, the rest of a specific reaction, as shown in Table 1. One reaction type represents several specific reactions if they have the same reaction centers.

2.3. Reaction Cores. If specific reactions have the same reaction centers, they will be processed further. A maximum common substructure associated with reaction centers is called a reaction skeleton; the rest of a specific reaction is an R-group. Reaction cores consist of reaction skeletons and R-groups. Some examples are listed in Table 2.

3. DERIVING GENERIC REACTION KNOWLEDGE

The method of deriving generic reaction knowledge described in the paper is based on the SSS algorithm and consists of several key steps: preprocess of strategic bonds, SSS, computation of R-groups' similarity, etc. The flowchart is shown in Figure 2.

3.1. Preprocess of Strategic Bonds. A strategic bond is the first bond changed/broken/made in the retrosynthetic analysis of a target molecule. Preprocessing strategic bonds is to decrease the search time for recognizing the strategic bonds in the target molecule and to increase the rate and accuracy for deriving the generic reaction knowledge. To minimize the consumption of atom-by-atom comparison, the nonstrategic bonds should be masked before SSS. Recogniz-

* Corresponding author phone: +86-21-54925266; fax: +86-21-54925264; e-mail: yaojh@mail.sioc.ac.cn

[†] Laboratory of Computer Chemistry and Chemoinformatics.

[‡] Graduate School of the Chinese Academy of Sciences.

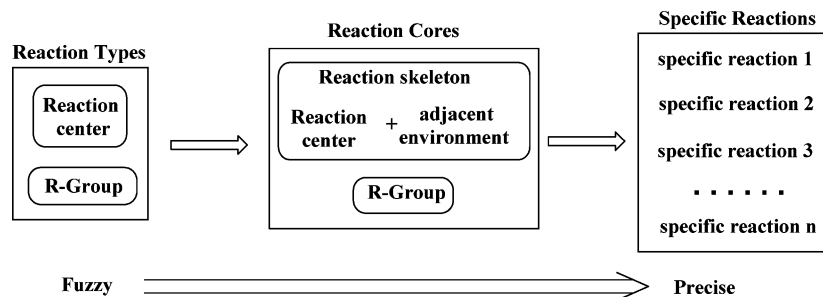


Figure 1. Reaction knowledge organized based on generic reactions.

Table 1. Two Examples of Reaction Type^a

No.	Reaction Type	Specific Reaction ¹
1	<p> $R_2-CH=CH-R_1 \longrightarrow$ </p> <p> $R_1:$ </p> <p> $R_2:$ </p>	<p>.....</p>
2	<p> $R_3-CH=CH-R_1 + R_2-C(=O)-R_3 \longrightarrow$ </p> <p> $R_1:$ </p> <p> $R_2:$ </p> <p> $R_3:$ </p>	<p>.....</p>

^a Reaction center is in bold.

ing strategic bonds has been studied in many retrosynthetic searching systems.⁶ The process is complicated and not easy to be implemented. The method described here is to simplify recognition of strategic bonds in the target molecule.

According to the results of analyzing a great deal of reaction data and seven rules⁷ for bridged polycyclic

structures in LHASA, the preprocess method presented in this paper concerns five rules for strategic ring bonds and one for strategic aliphatic bonds (Table 3).

Before superstructure searching, every candidate molecule is preprocessed by six rules, and all of the nonstrategic bonds will be indicated. The performance of deriving generic reac-

Table 2. Some Examples of Reaction Core^a

No.	Reaction Core	Specific Reaction ¹
1		
	R ₁ : R ₂ : 	
2		
	R ₁ : 	
3		
	R ₁ : 	

^a Reaction skeleton is in bold.

tion knowledge after preprocessing is improved. Three examples of preprocessing strategic bonds are listed in Table 4.

3.2. Recognition of Reaction Skeleton. The SSS presented in this paper has the reasonable extrapolating capability which traditional substructure searching does not have, because it includes two steps: recognition of reaction skeletons and computation of R-groups' similarity.¹¹ Recognition of reaction skeletons is an important requirement for judging if the known reaction can be applied to new compounds successfully, and comparison of R-groups can improve the usability.

Recognition of reaction skeletons is a subgraph isomorphism (in this paper, it corresponds to the superstructure search) which

is an NP-complete problem.¹² Unfortunately, there are no analogous polynomial algorithms for it. There are more than 100 000 generic reactions in the generic reaction knowledge base. If the subgraph isomorphism algorithm is solely employed in recognition of a reaction skeleton, the performance will not be acceptable. To improve the efficiency of the recognition, the "two steps" method¹³ is employed: (1) screening and (2) atom-by-atom comparison. The first step reduces the number of atom-by-atom comparison, and the entire generic reaction retrieval performance is significantly improved.

3.2.1. Screening. MACCS keys¹⁴ of MDL, powerful and efficient substructure descriptor codes, are selected from

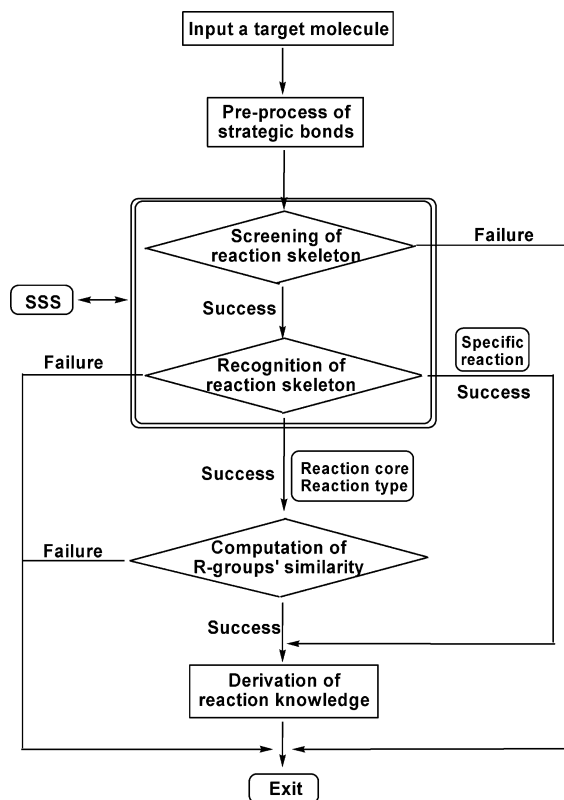


Figure 2. Flowchart of identifying generic reaction knowledge.

Table 3. Preprocess Rules and Corresponding Examples

No.	Pre-process rules	Examples	Remarks ^a
1	Aromatic bonds are not potentially strategic characters.		The bold bonds are non-strategic.
2	Any bond common to a pair of bridged or fused rings whose envelope is eight-membered or larger cannot be considered strategic.		The bold bond is non-strategic.
3	C-Hetero bonds in non-aromatic rings are strategic bonds.		The bold bonds are non-strategic.
4	A strategic bond must be attached to another non-three-membered ring.		The bold bonds are non-strategic.
5	A Carbon-Carbon single bond connected with the environment (limited as previously to topological distance=2 from the bond) without any non-common atom ^a is non-strategic.		The bold bonds are non-strategic.
6	A terminal carbon-carbon single aliphatic bond is a non-strategic bond.		The bold bond is non-strategic.

^a A common atom is an atom that fulfills the following three criteria: (1) it must be a carbon atom; (2) all its neighbor atoms must be carbon atoms; and (3) every bond between these atoms must be a single bond. Otherwise, this atom will be called a noncommon atom.³ ^b The remark of an example only corresponds to its preprocess rule.

numerous structure fragments. These keys as fingerprints in structure searching are successfully applied not only to MACCS system¹⁵ but also in some reported applications.^{16,17} Thus, a set of fingerprints selected from MACCS keys are employed in our work.

3.2.2. Fingerprints Design. To select proper fingerprints from 166 MACCS keys, 60 000 reactions randomly selected from the MDL reaction database¹ were used to test these keys. The result is depicted in Figure 3, and the occurrence frequency of some of MACCS keys is listed in Table 5.

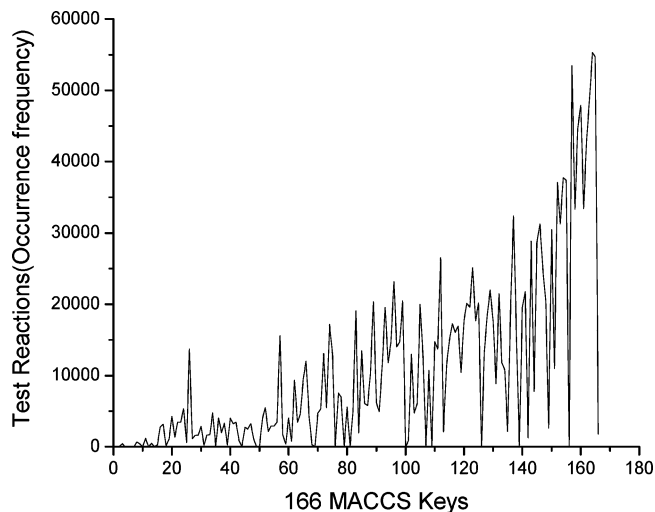


Figure 3. Occurrence frequency of 166 MACCS keys.

Table 4. Results of Preprocessing Strategic Bonds

	Stipiamide ^a	Roseophilin ^a	OkinonellinB ¹⁰
Before pre-processing			
After pre-processing ^a			

^a The bold bonds are nonstrategic.

Table 5. Some of MACCS Keys and Their Occurrence Frequencies^a

MACCS keys	frequency	MACCS keys	frequency
ISOTOPE	51	OC(N)C	11453
QAAA@1	694	CN(C)C	13457
GROUP IVA, VA, VIA	447	GROUP VIII	433
PERIODS 4–6			
ACTINIDE	0	X!A\$A	5790
GROUP IIIB, IVB	1	S	10170
LANTHANIDE	1	OAAAO	20343

^a “A” for any atom except hydrogen; “Q” for any atom except carbon and hydrogen; “X” for any halogen atom; “@” indicates that an atom number (*n*) is attached; “\$” indicates that the bond is part of a ring; “!” indicates that the bond is part of a chain.

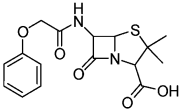
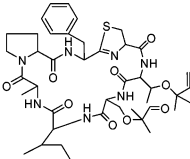
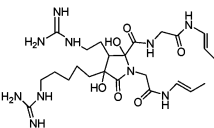
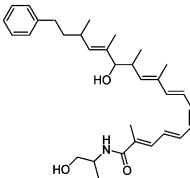
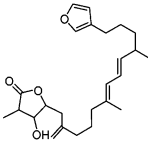
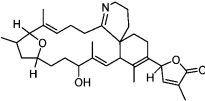
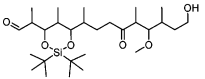
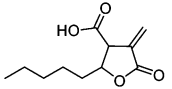
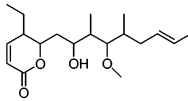
Figure 3 indicates the occurrence frequency of describing the 60 000 reactions by 166 MACCS keys. In general, the keys with higher occurrence frequency are more powerful in fingerprints design. 128 MACCS keys with more descriptive capability for reaction information are selected in SSS.

3.2.3. Atom-by-Atom Comparison. Atom-by-atom comparison is the second stage in the SSS. Ullmann algorithm¹⁸ is employed.

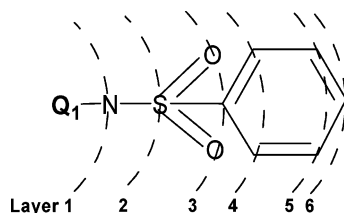
Originally, the Ullmann algorithm was designed to solve the problem of subgraph isomorphism and detecting groups. The algorithm is a depth-first tree-search for exhaustive enumeration.

3.2.4. Test for the Effect of Fingerprints. If most of the nonhit products in the generic reaction knowledge base can

Table 6. Testing Results of Screening Efficiency

Target Molecules	Number of generic reactions derived			Time ^a	
	Screening	Atom-by-atom comparison	Screening + Atom-by-atom comparison	Atom-by-atom comparison	Screening + Atom-by-atom comparison
penicillium ¹⁹					
	134	11	11	59m 2s	2m 19s
TrunkamideA ²⁰					
	147	18	18	60m 18s	2m 32s
AnchinopetolideD ²¹					
	170	27	27	60m 24s	2m 15s
Stipiamide ⁸					
	125	31	31	61m 11s	2m 15s
OkinonellinB ¹⁰					
	19	3	3	59m 50s	2m 25s
Gymnodimine ²²					
	24	12	12	60m 50s	2m 36s
Scytophycin ²³					
	59	17	17	62m 0s	3m 7s
Methylenolactocin ²⁴					
	97	2	2	62m 37s	3m 4s
Pironetin ²⁵					
	100	11	11	64m 17s	1m 32s

^a The configuration of the platform used is CPU: Intel Pentium 4A/2.0G; RAM: 256M; OS: Windows 2000.

Chart 1. One R-Group

be filtered during the screening process, the times of atom-by-atom comparison will be decreased, and the performance of deriving generic reaction knowledge will be improved.

About 100 different compounds, such as penicillium, trunkamide A, anchinopetolide, and the generic reaction knowledge base including 135 670 generic reactions are used for testing performance. A part of the results is listed in Table 6. According to Table 6, the effect of fingerprints is proved: 1. The number of generic reactions derived after screening is much less than generic reactions in a generic reaction knowledge base, i.e., a few of the molecules in the generic reaction knowledge base that match the target molecule have been identified after screening. 2. Hits for “screening+atom-by-atom comparison” is the same as that for “atom-by-atom comparison”. 3. The search time for “screening+atom-by-atom comparison” is much less than that for “atom-by-atom comparison”.

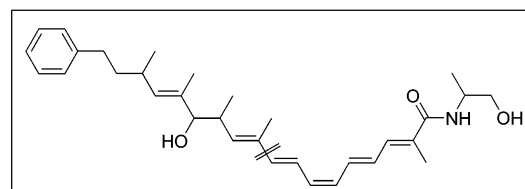
3.3. Computation of R-Group's Similarity.¹¹ Each R-group is described by several descriptors, such as topological distance, electronegativity, hydrogen-bond acceptor, and hydrogen-bond donor etc., which affect reactions obviously and can be calculated conveniently.

Structural descriptors for describing the R-group in Chart 1 are listed in Table 7. Computation of the R-groups' similarity consists of three steps: (1) normalization of information described by descriptors; (2) calculation of the distances between each R-group and the barycenter of the set of R-groups compared; and (3) comparison of their similarities based on the distances calculated in step (2).

Table 7. Structural Descriptors for Describing the R-Group in Chart 1

descriptors	layer					
	1	2	3	4	5	6
atomic mass ^a	15.01	32.07	44.01	26.03	26.04	12.01
electronegativity ^b	3.05	2.6	8.7	5.2	5.2	2.6
ring size ^c	0	0	6	12	12	6
aromaticity ^d	0	0	1	2	2	1
hydrogen bond acceptor ^e	1	1	2	0	0	0
hydrogen bond donor ^f	1	0	0	0	0	0
valence bond ^g	1	2	8	8	8	4
number of Q ^h	1					
ring size of Q ⁱ	0					
hybridization of Q ^j	1					

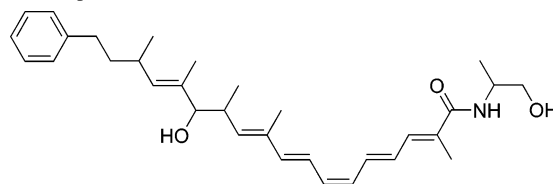
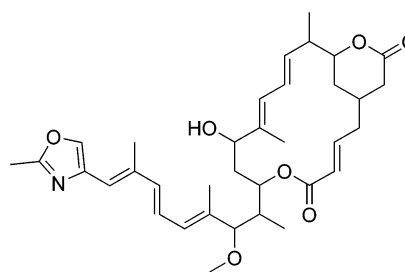
^a The atomic mass in the periodic table. ^b Electronegativity of each atom.²⁶ ^c Total number of the ring size of all atoms. The largest one where an atom is used. ^d 1: aromatic atom; 0: non_aromatic atom. ^e The number of hydrogen bond acceptors. ^f The number of hydrogen bond donors. ^g 1: single bond, 2: double bond, 3: triple bond, 4: aromatic bond. Total number of bonds connected with the atoms at the layer. Priority order: aromatic bonds > triple bonds > double bonds > single bonds. The highest priority of an atom is used. ^h The number of points connected with the reaction skeleton in an R-group. ⁱ The number of the ring size connected with an R-group. ^j Hybridization of each point connected with the reaction skeleton in an R-group (Sp³: 1, Sp²: 2, Sp: 3)

**Figure 4.** The result of splitting stipiamide.**Table 8.** Test Results of Preprocess Strategic Bonds for Stipiamide

	preprocessing strategic bonds + SSS	SSS
number of generic reactions derived	30	31
search time	1m 44s	1m 58s

Table 9. Invalid Generic Reaction Knowledge for Synthesis of Stipiamide

Target structure	Generic reaction knowledge

Chart 2. Stipiamide**Chart 3.** Rhizoxin D

3.3.1. Normalization. Each R-group is described by properties of atoms and bonds and their topological distances. They consist of 45 structural descriptors which correspond to 45 dimensions of a space.¹¹ The ranges of descriptors values are different. The goal of normalization is to make all the descriptors have the same value range. Then the similarity can be computed reasonably.

3.3.2. Calculation. The distance between two arrays of structural descriptors is computed in (1)

$$\text{distance} = \left[\sum_{i=1}^{10} \sum_{j=1}^6 (d_{A_j}^i - d_{B_j}^i)^2 \right]^{(1/2)} \quad (1)$$

Table 10. Some Valid Generic Reaction Knowledge for Synthesis of Stipiamide^a

No.	Target structure	Generic reaction knowledge
1		
2		
3		
4		
5		
6		
7		
8		
9		

^aThe bonds in bold black indicate that they are matched with the product in the generic reaction derived, and they are strategic bonds.
 “*” indicates the reaction is taken from ref 8.

Table 11. Test Results of Preprocessing Strategic Bonds for Rhizoxin D

	preprocessing strategic bonds + SSS	SSS
number of generic reactions derived	14	16
search time	3m 18s	3m 52s

where i is for a R-group's descriptor; j is for a layer; d_{Aj}^i stands for the accumulated values describing the atoms in the j th layer in the R-group (A) by the i th descriptor; d_{Bj}^i is the same as d_{Aj}^i .

3.3.3. Comparison. To compare an R-group in the target molecule with a set of R-groups in the generic reaction knowledge base, we follow four steps protocol as follows:

1. Obtain the barycenter ($X_1, X_2, X_3, \dots, X_{45}$) for the set of R-groups in the generic reaction knowledge base by (2)

$$X_m = \sum_{i=1}^n x_{im}/n \quad (1 \leq m \leq 45, n > 0) \quad (2)$$

where x_{im} is the m th descriptor of the i th R-group, and n is the total number of R-groups in the knowledge base compared with that in the query.

2. Calculate the distances between the barycenter and each R-group in the set of R-groups in the knowledge base; get the maximum distance (Max_Distance) among the distances calculated by (1).

3. Calculate the distances between the barycenter and the R-group in the target molecule (QR1_Core) by (1).

4. Compare these distances: QR1_Core and Max_Distance. If QR1_Core is in the range $[0, \text{Max_Distance}]$, the R-group can be considered sufficiently similar to those in the knowledge base.

Table 12. Some Valid Generic Reaction Knowledge for Synthesis of Rhizoxin D^a

No.	Target molecule	Generic reaction knowledge
1		
2		
3		
4		

^a The bonds in bold black indicate that they are matched with the product in the generic reaction derived, and they are strategic bonds. “*” indicates that the reaction is taken from ref 27.

4. EXPERIMENTS

After preprocessing strategic bonds, the recognition of reaction skeletons and the computation of R-groups' similarity for the target molecule, the relevant generic reactions can be derived. The generic reaction knowledge deriving process is iterated in the three steps as mentioned above. The method reported in this paper has been tested. Two examples are shown as the following.

Example 1. Stipiamide.⁸ The structure is shown in Chart 2. The time for deriving the generic reaction knowledge of stipiamide is listed in Table 8. The table indicates that the searching performance has been improved by marking strategic bonds and recognizing nonstrategic bonds in preprocess. In Table 9, the generic reaction knowledge derived without preprocessing strategic bonds has no synthetic significance for stipiamide. It proves that nonstrategic bonds can be omitted by preprocess.

In Table 10, nine valid generic reactions are listed. Some of them are similar to the ones in ref 8. According to the generic reaction knowledge, the target molecule can be split into the reasonable synthetic precursors. For example, according to the first generic reaction knowledge derived, stipiamide is split into two precursors shown in Figure 4. At last, the synthetic route of the target will be obtained.

Example 2. Rhizoxin D.²⁷ Chart 3 shows the rhizoxin D structure. The results of preprocessing strategic bonds are shown in Table 11. From the data, we can see that the searching performance is improved by preprocessing strategic bonds as we have done in example 1. Some valid generic reaction knowledge for rhizoxin D is listed in Table 12.

Only four results are listed for rhizoxin D in Table 12. There are also some searching results which are similar to the ones in ref 27. The generic reactions derived can be used to split rhizoxin D into reasonable synthetic precursors which can derive generic reaction knowledge again. If these steps are repeated, the synthetic route for rhizoxin D can be also obtained. For a given target, the synthesis design can be completed by deriving generic reaction knowledge iteratively.

5. CONCLUSION

In this paper, we present the superstructure searching algorithm for deriving generic reaction knowledge which is helpful for synthesis design.

The test results indicate the method used to deriving generic reaction knowledge is very fast and robust. Because the number of reactions in the generic reaction knowledge base is much less than known reactions in nature, the results are not the same as what are published. A lot of reactions will be saved in the generic reaction knowledge base. The work described in this paper is the foundation for synthesis planning; further work will be published in the future.

ACKNOWLEDGMENT

This work was supported in part by the National Basic Research Program (also called the 973 Program) of China, through Grant 2003CB114401, and by the Chinese Academy of Sciences, through Grants KGCX2-SW-213-05 and KGCX2-SW-213-01. The authors are thankful to Dr. J. Xu for his help with the English language.

REFERENCES AND NOTES

- (1) MDL Reaction Database, MDL Information Systems, Inc. <http://www.mdli.com>.
- (2) Wipke, W. T.; Rogers, D. Artificial intelligence in organic synthesis. SST: starting material selection strategies. An application of superstructure search. *J. Chem. Inf. Comput. Sci.* **1984**, *24*, 71–81.
- (3) Wang, K.; Wang, L. S.; Yuan, Q.; Luo, S. W.; Yao, J. H.; Yuan, S. G.; Zheng, C. Z.; Brandt, J. Construction of a generic reaction knowledge base by reaction data mining. *J. Mol. Graphics Modell.* **2001**, *19*, 427–433.
- (4) Zhu, Q.; Yao, J. H.; Li, F.; Chen, H. F.; Yuan, S. G. A Novel Approach to Acquire Reaction Knowledge by Classification of Reaction Data. *Acta Chim. Sin.* **2004**, *62*, 112–119 (in Chinese).
- (5) The bond crossed by a double oblique line is a reacting center; it means a broken bond in reactants and a formed one in products. The single crossed line on a bond is indicating that the bond has been changed; it might be changed from a double bond to a single bond or a triple bond to a double bond, etc.
- (6) <http://www2.chemie.uni-erlangen.de>.
- (7) Corey, E. J.; Jeffrey, H. W.; Orf, H. W.; Pensak, D. A.; Petersson, G. General methods of synthetic analysis. Strategic bond disconnections for bridged polycyclic structures. *J. Am. Chem. Soc.* **1975**, *97*, 6116–6124.
- (8) Andrus, M. B.; Lepore, S. D.; Turner, T. M. Total Synthesis of Stipiamide and Designed Polyenes as New Agents for the Reversal of Multidrug Resistance. *J. Am. Chem. Soc.* **1997**, *119*, 12159–12169.
- (9) Fürstner, A.; Weintritt, H. Total Synthesis of Roseophilin. *J. Am. Chem. Soc.* **1998**, *120*, 2817–2825.
- (10) Schmitz, W. D.; Messerschmidt, N. B.; Romo, D. A γ -Lactone-Based Strategy Applied to the Total Synthesis of (8S,21S,22S,23R)- and (8R,21S,22S,23R)-Okiononellin B. *J. Org. Chem.* **1998**, *63*, 2058–2059.
- (11) Zhu, Q.; Yao, J. H.; Li, F.; Chen, H. F.; Yuan, S. G. Comparison of the R-Group Similarity. *Acta Chim. Sin.* **2004**, *62*, 1585–1589 (in Chinese).
- (12) Stobaugh, R. E. Chemical substructure searching. *J. Chem. Inf. Comput. Sci.* **1985**, *25*, 271–275.
- (13) Willett, P. *Three-dimensional chemical structure handling*; Research Studies Press Ltd.: 1991; pp 5–14.
- (14) MACCS Keys, MDL Information Systems Inc., 14600 Catalina Street, San Leandro, CA 94577, U.S.A.
- (15) Wipke, W. T.; Dill, J. D.; Peacock, S.; Hounshell, D. Search and Searching Using an Automated Molecular Access System; 182nd National Meeting of the American Chemical Society, New York, Aug, 1981.
- (16) McGregor, M. J.; Pallai, P. V. Clustering of Large Databases of Compounds: Using the MDL "Keys" as Structural Descriptors. *J. Chem. Inf. Comput. Sci.* **1997**, *37*, 443–448.
- (17) Xue, L.; Bajorath, J. Accurate Partitioning of Compounds Belonging to Diverse Activity Classes. *J. Chem. Inf. Comput. Sci.* **2002**, *42*, 757–764.
- (18) Ullmann, J. R. An Algorithm for Subgraph Isomorphism. *J. Assoc. Comput. Match.* **1976**, *23*, 31–42.
- (19) Sheehan, J. C.; Henery-Logan, K. R. The Total Synthesis of Penicillin V. *J. Am. Chem. Soc.* **1959**, *81*, 3089–3094.
- (20) Wipf, P.; Uto, Y. Total Synthesis and Revision of Stereochemistry of the Marine Metabolite Trunkamide A. *J. Org. Chem.* **2000**, *65*, 1037–1049.
- (21) Casapullo, A.; Minale, L.; Zollo, F.; Lavayre, J. Four New Dimeric Peptide Alkaloids, Anchinopeptolides B–D, and Cycloanchinopeptolide C, Congeners of Anchinopeptolide A, from the Mediterranean Marine Sponge *Anchinoe tenacior*. *J. Nat. Prod.* **1994**, *57*, 1227–1233.
- (22) Yang, J.; Cohn, S. T.; Romo, D. Studies toward (–)-Gymnodimine: Concise Routes to the Spirocyclic and Tetrahydrofuran Moieties. *Org. Lett.* **2000**, *2*, 763–766.
- (23) Grieco, P. A.; Speake, J. D.; Yeo, S. K.; Miyashita, M. Synthesis of the C(19)–C(32) fragment of scytopycin C via stereospecific methylation of γ,δ -epoxy acrylates with trimethylaluminum. *Tetrahedron Lett.* **1998**, *39*, 1125–1128.
- (24) Mandal, P. K.; Maiti, G.; Roy, S. C. Stereoselective Synthesis of Polysubstituted Tetrahydrofurans by Radical Cyclization of Epoxides Using a Transition-Metal Radical Source. Application to the Total Synthesis of (±)-Methylenolactocin and (±)-Protolichesterinic Acid. *J. Org. Chem.* **1998**, *63*, 2829–2834.
- (25) Gurjar, M. K.; Chakrabarti, A.; Rama Rao, A. V. A Stereocontrolled Synthesis of Pironetin. *Heterocycles* **1997**, *45*, 7–10.
- (26) Dean, J. A. *Lange's Handbook of Chemistry*, 15th ed.; 1999; p 4.29.
- (27) Williams, D. R.; Werner, K. M.; Feng, B. Total Synthesis of Rhizoxin D. *Tetrahedron Lett.* **1997**, *38*, 6825–6828.

CI0496402