chromatography on silica gel (CH_2Cl_2 as eluant) gave a *cis*/*trans* mixture of 4-phenyl-1-cyclohexanol (159 mg, 0.91 mmol, 91 % yield; *cis*:*trans* = 23:77).

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[9] a) K. G. Akamanchi, N. R. Varalakshmy, *Tetrahedron Lett.* **1995**, *36*, 3571; b) K. G. Akamanchi, N. R. Varalakshmy, *Tetrahedron Lett.* **1995**, *36*, 5085; c) K. G. Akamanchi, N. R. Varalakshmy, B. A. Chaudhari, *Synlett* **1997**, 371.
[10] a) T. Ooi, M. Takahashi, K. Maruoka, *J. Am. Chem. Soc.* **1996**, *118*, 11307; b) T. Ooi, E. Tayama, M. Takahashi, K. Maruoka, *Tetrahedron Lett.* **1997**, *38*, 7403; c) T. Ooi, A. Saito, K. Maruoka, *Tetrahedron Lett.*, in press.
[11] The reduction of benzaldehyde with $Al(OiPr)_3$ (1 equiv) in 2-propanol did not proceed at room temperature.
[12] Our system surely takes advantage of the lower susceptibility of both acetone and acetophenone toward the MPV reduction with the reduction products as a hydride source. Indeed, attempted reaction of acetone with 4-phenylcyclohexanol (1 equiv) in the presence of **1** (5 mol %) in CH_2Cl_2 at room temperature for 1 h gave rise to 4-phenylcyclohexanone in only 8 % yield.
[13] J. D. Morrison, H. S. Mosher, *Asymmetric Organic Reactions*, American Chemical Society, Washington, DC, **1976**, p. 160. Evans et al. reported the first catalytic and highly enantioselective MPV reduction with a chiral Sm complex: D. A. Evans, S. G. Nelson, M. R. Gagne, A. R. Muci, *J. Am. Chem. Soc.* **1993**, *115*, 9800.
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[15] Unfortunately, the asymmetric MPV reduction of dialkyl ketones gave unsatisfactory results in terms of reactivity and selectivity. For example, reaction of 2-undecanone under similar conditions with (*R*)-(+)-*sec*-*o*-bromophenethyl alcohol afforded 2-undecanol in 11 % yield with less than 25 % *ee*.
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The Family Approach to the Resolution of Racemates **

Ton Vries,* Hans Wynberg,* Erik van Echten, Jan Koek, Wolter ten Hoeve, Richard M. Kellogg, Quirinus B. Broxterman,* Adri Minnaard, Bernard Kaptein, Sietse van der Sluis,* Lumbertus Hulshof, and Jaap Kooistra

A cornerstone of stereochemistry is the resolution of tartaric acid by Louis Pasteur.[1, 2] This conversion of a racemate with a chiral resolving agent and subsequent separation of the mixture of diastereomers formed is known as the "classical method of resolution",[3] and remains, 150 years after Pasteur, a paradigm of trial and error.[4] Despite many attempts,[3] neither computer-assisted modeling,[5] detailed examination of the crystal structure data of diastereomeric salts,[6] study of the energy differences of diastereomeric salts,[7] nor empirical correlations[8] have led to a hypothesis, let alone a theory, on which to base a predictable resolution technique.

All too aware of these problems on the basis of long experience and motivated by a need to develop fast and reliable protocols, we considered the combinatorial approach, a recent technique that has shown promise in the search for lead compounds in drug design.[9] A rudimentary application of such methodology led to the remarkable results reported here.

The standard technique for the resolution of a racemate entails the addition of one chiral resolving agent to a racemate followed by a suitable waiting period in order to observe crystallization of one diastereomeric salt. We hoped that the simultaneous addition of several resolving agents might shorten the time required for the hit-and-miss method of finding a resolving agent. The addition of more than one resolving agent could result in the precipitation of the least soluble diastereomeric salt, thus obviating the need for repetition of the process of resolution with one resolving agent at a time. To our great surprise, the simultaneous addition of more than one member of a "family" of resolving agents (for a definition, see below) to a solution of a racemate usually causes very rapid precipitation of a crystalline diastereomeric salt in good to high enantiomeric purity and yield. The results from some of the more than two hundred successful experiments carried out during the past year[10] are listed in Tables 1 and 2. In virtually all cases examined both the yields and enantiomeric excesses (*ee*) were superior to those obtained by the classical approach (compare entry 55 with entry 53).

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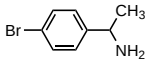
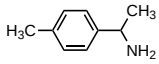
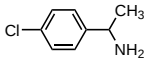
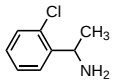
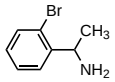
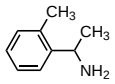
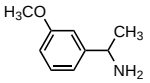
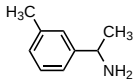
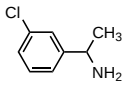
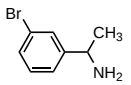
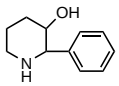
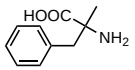
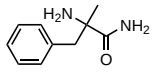
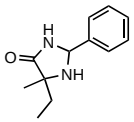
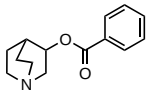
Table 1. Resolutions with mixtures of related reagents—the "family" approach.

Entry	Substrate	Reagent mix	Solvent[a]	Number of recryst. (solvent)	*ee* [%]	HPLC[b]	Reagent ratio[c]
1		**M**	A	1 (A)	96	1	1:5:0
2		**P**	A	1 (C)	98	1	–[e]
3		**M**	C	1 (D)	94	1	1:5:0
4		**P**	A	1 (A/B)	99	1	20:0:1
5		**M**	A/C	1 (C)	90	1	1:1[d]
6		**M**	A/C	1 (A/C)	90	2[g]	1:1[d]
7		**M**	A/C	1 (A/C)	94	1	1:10[d]
8		**P**	A/C	1 (C)	99	1	5:5:1
9		**M**	A/C	1 (C)	99	1	1:4[d]
10		**M**	A/C	1 (C)	99	1	1:4[d]
11		**T**	C	1 (C)	99		5:1:1
	cis						
12		**P**	B	1 (C)	92	1	4:1:2
13		**P**	A	1 (A)	98	1	2:1:3
14		**P**	A	1 (A/D)	98	1	4:1:0
	cis/*trans*						
15		**P**	A/D	1 (A/D)	66	2[f]	1:1:2
16		**T**	D	1 (D/G)	98	2	1:10:4

The surprising discovery that the precipitate contained more than one component of the mixture of resolving agents was readily established and checked quantitatively by means of ^{1}H NMR spectroscopy, HPLC, or GC. Equally surprising was that the unusual nonstoichiometric compositions of the diastereomeric salts were retained even after several crystallizations. The ratio in the mixed salt of the two mandelic acid derivatives used for resolution (entry 25) was 1:3.7 after five recrystallizations (1:3.1 after a single recrystallization). Only on repeated recrystallization (sometimes more than ten times) did the composition of these salts begin to change to the standard 1:1 ratio of acid to base. Some salts retained their nonstoichiometric composition even after 20 recrystallizations. The ratio of the three phosphoric acids in the mixed salt of entry 26 was 1:14:55 after 20 recrystallizations.

Random combinations of resolving agents generally gave only moderate yields. The development of a principle of "families of resolving agents" was greatly aided by the fact that we had available in our laboratory an entire "family" of chiral phosphoric acids, based on the discovery of these acidic resolving agents 12 years ago.[11] The members of a family in general bear strong structural similarity and are stereochemically homogeneous (homochirality among family members and enantiomeric purity of the components). The combinations used for the current work were generally referred to in terms of coded "mixes", the compositions of which are illustrated in Scheme 1 (page 2254). Usually, although not exclu-

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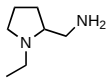
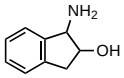
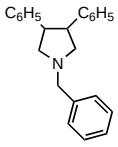
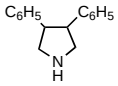
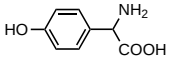
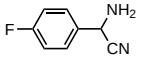
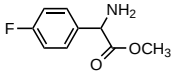
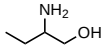
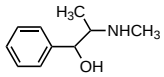
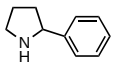
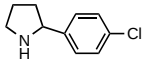
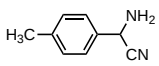
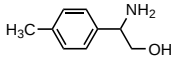
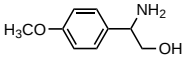
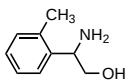
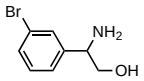
Table 1. (Continued).

Entry	Substrate	Reagent mix	Solvent[a]	Number of recryst. (solvent)	*ee* [%]	HPLC[b]	Reagent ratio[c]
17		**P**	A	2 (A/C)	89	2[f]	4:1:0
18	 *cis*	**PGA**	F	1 (F/A)	96	4	1:1.8:0.8
19	 *trans*	**T**	C	1 (C)	97	2	6:1:1
20		**T**	A	1 (A/D)	99	2[g]	1:3:3
21		**P**	B/G	1 (B/G)	95	1	1:2:3
22		**P**	A	1 (A)	98	2	20:2:1
23		**P**	A	1 (B)	94	1	15:3:2
24		**T**	B	2 (B)	96	2[g]	0:2:1
25		**M**	A	1 (A)	98	2[g]	1:3.1[d]
26	 *erythro*	**P**	C	1 (C)	98	1	1:1.2:1.1
27		**P**	C	1 (C)	93	1	–[e]
28		**P**	C	1 (C)	96	2[g]	2:7:4
29		**P**	B/G	–	95	1	10:1:1
30		**P**	A	1 (B)	91	1	10:1:1
31		**P**	C	–	97	1	7:1:1
32		**M**	A	–	99	1	1:4:1
33		**P**	C	–	99	1	1:0:0[h]

sively, the components of a family of resolving agents differ in the substitution pattern on an aromatic ring.[12] An exception is the **PE-III** mix, whose members differ in the side chain.

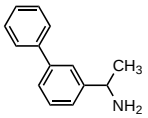
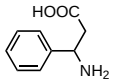
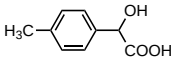
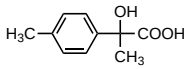
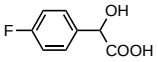
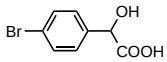
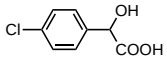
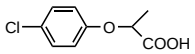
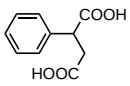
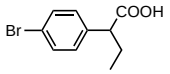
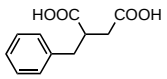
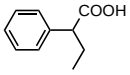
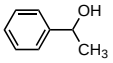
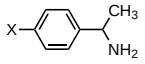
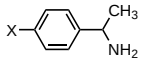
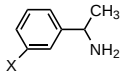
The current definition of a family is clearly not complete, and it is evident that many more families are possible. Eliel and Wilen[13] list over 100 resolving agents, many of which could lend themselves to the preparation of a family. Note, for example, that tartaric acid does not belong to the family of benzoyltartaric acids.[14]

Probably the most significant, as well as startling, feature of this new method for the resolution of racemates is the extremely high success rate, defined in terms of yield and enantiomeric excess in a first trial. We have resolved over 100 racemates, predominantly acids and bases, during the past year and have found only three that resisted resolution by the family approach. The failures appear to be due solely to lack of salt formation. This can occur in some cases when the racemate displays either steric hindrance or weak basicity or acidity, thus preventing salt formation with the relatively weak resolving acids or bases. This problem is being addressed by adding a family of stronger acids and bases to our list.

The most significant findings are as follows:

1) On addition of two or more resolving agents of a family to a racemate, rapid crystallization of a diastereomeric salt containing different family members takes place in good to excellent yield. The enantiomeric excess of the recovered enantiomer approaches 100% in many cases or is usually attained after one recrystalliza-

Table 1. (Continued).

Entry	Substrate	Reagent mix	Solvent[a]	Number of recryst. (solvent)	*ee* [%]	HPLC[b]	Reagent ratio[c]
34		**P**	A	1 (C)	86	3	–[e]
35		**P**	A	–	98	1	5:4:1
36		**PE-II**	A/D	1 (B/D)	99	2	1:4
37		**PE-I**	F	1 (F)	97	2	–[e]
38		**PE-II**	A	–	99	2	–[e]
39		**PE-II**	A	1 (A/D)	99	2	15:1:0
40		**PE-II**	A	1 (A/D)	95	2	35:1:0
41		**PE-I**	E	1 (E)	88	2	–[e]
42		**PG**	C	1 (B)	97	3	–[e]
43		**PE-II**	A	1 (C)	95	2	1:0:0
44		**PE-II**	A	1 (C)	88	3	2:2:1
45		**PG**	C	1 (C)	93	2	–[e]
46		**TA**	H	–	82	3	1:1
47	 X = Cl, Me, Br (1:1:1)	**M2**/**M3**	B	1 (B)	98	1	1:1:1 (amines), 1:1 (acids)
48	 X = Cl, Me, Br (1:1:1)	**M2**/$PhCH_2CO_2H$	B	1 (B/G)	98	1	1:1:1, contains both acids
49	 X = OMe, Cl, Br (1:1:1)	**M2**	B	–	98	1	2:4:4

[a] A: 2-butanone; B: ethanol; C: 2-propanol; D: methanol; E: ethyl acetate; F: toluene; G: water; H: hexane. [b] HPLC columns: 1: Crownpak Cr; 2: Chiralpak AD; 3: Chiralcel OD; 4: Chiralcel OB; 5: Chiralcel OJ; 6: R,R Whelk; 7: Ultron ES OVM. [c] The order given refers to the notation as indicated in the Experimental Section. [d] Only with **M1**/**M2**. [e] Could not be accurately determined by ^{1}H NMR spectroscopy, but three components were present. [f] HPLC analysis of the benzoate. [g] HPLC analysis of the tosylate. [h] **P2** and **P3** could not be detected by ^{1}H NMR spectroscopy (200 MHz).

tion (see Table 1). In this respect the work of Lahav and Addadi is highly pertinent to the phenomena observed here.[15] The solubility behavior of the mixed salts warrants further study.

2) The high rate of success makes the method of commercial value. This new technique for the resolution of racemates, including the recovery of the resolving agent(s), is identical to that currently used in the laboratory and in industrial processes, except for the simultaneous use of multiple resolving agents. It proved most effective to carry out a resolution with a 1:1 or 1:1:1 mixture chosen from the family of resolving agents.

3) In illustration of the potential—and at the same time the complexity—of the method, it is possible to incorporate a racemic family member (Table 2, entries 51 and 52), a family member of the opposite absolute configuration (entry 54), and even an achiral family member (entry 56).

4) The method is applicable to resolutions through formation of molecular complexes using, for example, TADDOL derivatives (entry 46).[16]

5) Mixtures of racemates can be resolved to enantiomerically pure mixtures either with a single resolving agent (entry 49) or with several resolving agents (entries 47 and 48).

The composition of the diastereomeric salts clearly deserves further study. The crystal structure of the mixed salt from (+)-(1*S*,2*R*)-ephedrine (100%), (−)-(*R*)-phencyphos (**P1**, 52.5%), and (−)-(*S*)-chlocyphos (**P2**, 47.5%) was determined. It was composed of a random distribution of the two resolving agents, which is seen as an average unit cell.

Furthermore, the unusual and unpredictable nonstoichiometric composition of the

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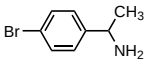
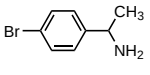
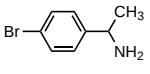
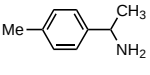
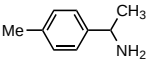
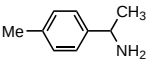
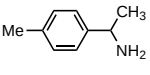
Table 2. Resolutions with mixtures containing racemic reagents, achiral reagents, and reagents with opposite configuration.

Entry	Racemate	Acid	Acid	*ee* (acid) [%]	*ee* (amine) [%]	Ratio of acids
50		**M1** (*S*)	**M2** (*S*)	–	84	1:1
51		**M1** (*S*)	**M2** (rac.)	95 (*S*)-**M2**	90	4:3
52		**M1** (rac.)	**M2** (*S*)	95 (*S*)-**M1**	99	3:4
53 1:4		**M1** (*S*)	**M2** (*S*)	–	–	87
54		**M1** (*R*)	**M2** (*S*)	–	90	1:6
55		–	**M2** (*S*)	–	57	–
56		–	**M2** (*S*) (0.5 equiv.) $PhCH_2CO_2H$ (0.5 equiv.)	–	90	contains both acids

diastereomeric salts appears to mirror to some extent findings in other fields.[17] The recent use of "cocktails", mixtures of drugs, to treat a disease bears interesting resemblance to our approach to resolutions. In an early and insightful comment[6] Walkinshaw refers to the close analogy between the drug–receptor nonbonding interactions and those present during resolution phenomena.

The use of a family of agents for the resolution of racemates effectively changes the trial-and-error method of resolution into an acceptable and almost routine practice. The consequences of this novel approach for other fields of inquiry also need to be explored.

Experimental Section

General procedure for the small-scale resolution of amines or acids with reagent mixes: To a solution of a racemic substrate (3 mmol) in the appropriate solvent was added one equivalent of a mix (1 mmol of each component, e.g. **P1**–**P3**). The mixture was heated to reflux and allowed to cool to room temperature. The salt was collected and analyzed with ^1H NMR spectroscopy to determine the composition. HPLC analysis was used to determine the enantiomeric excess of the substrate. The salt obtained was recrystallized from the appropriate solvent(s) until a clear solution was obtained. The mixture was cooled to room temperature, and the salt again analyzed.

Preparation of the mixes: Unless otherwise stated all resolution mixes used were enantiopure.

P mix: Phencyphos (**P1**, 2-hydroxy-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane,), chlocyphos (**P2**, 4-(2-chlorophenyl)-2-hydroxy-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane), and anicyphos (**P3**, 2-hydroxy-4-(2-methoxyphenyl)-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane) were prepared and resolved according to standard procedures.

T mix: Dibenzoyltartaric acid (**T1**) and di-*p*-toluoyltartaric acid (**T2**) were obtained from Aldrich, and di-*p*-anisoyltartaric acid (**T3**) was prepared according to a standard procedure.

M mix: Mandelic acid (**M1**) was obtained from Aldrich, *p*-methylmandelic acid (**M2**) and *p*-bromomandelic acid (**M3**) were prepared from the corresponding acetophenones and resolved with phenylethylamine.

PE-I mix: 1-(*p*-Chlorophenyl)ethylamine (**PE2**), 1-(*p*-bromophenyl)ethylamine (**PE3**), and 1-(*p*-methylphenyl)ethylamine (**PE4**) were prepared by a Leuckart synthesis from the commercially available acetophenones. For resolution of the mix, see entries 47 and 48 in Table 1.

PE-II mix: Nitration of enantiomerically pure phenylethylamine with HNO_3 provided a mixture that contained phenylethylamine (**PE1**), **1**-(*o*-nitrophenyl)ethylamine (**PE5**), and 1-(*p*-nitrophenyl)ethylamine (**PE6**) in equal amounts.

PG mix: Enantiomerically pure 2-amino-2-phenylethanol (**PG1**) was obtained by reduction of the phenylglycine methyl ester. Racemic 2-amino-2-(*p*-methylphenyl)ethanol (**PG2**) and 2-amino-2-(*p*-methoxyphenyl)ethanol (**PG3**) were obtained by reduction of the corresponding phenylglycines and resolved with phencyphos (**P1**).

PE-III mix: 1-Phenylethylamine (**PE1**) was obtained from Aldrich. α-Isopropylbenzylamine and α-ethylbenzylamine were prepared from the corresponding ketones by a Leuckart synthesis. The **PE-III** mix was obtained by resolution with phencyphos (**P1**).

PGA mix: The *N*-benzoylphenylglycines were obtained by Schotten–Baumann acylation of (*S*)-phenylglycine with benzoyl, *p*-toluoyl, and *p*-anisoyl chloride.

TA mix: (4*R*,5*R*)-2,2-Dimethyl-$\alpha,\alpha,\alpha',\alpha'$-tetraphenyl-1,3-dioxolane-4,5-dimethanol (TADDOL, **TA1**) and (4*R*,5*R*)-$\alpha,\alpha,\alpha',\alpha'$-tetra(*p*-methoxyphenyl)-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol (**TA2**) were prepared according to standard procedures.

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German version: *Angew. Chem.* **1998**, *110*, 2491–2496

Keywords: chirality · chiral resolution · enantiomeric resolution · combinatorial chemistry

[1] L. Pasteur, *Ann. Chim. Phys.* **1848**, *24*, 442–459.
[2] L. Pasteur, *C. R. Hebd. Seances Acad. Sci.* **1853**, *37*, 162–169.
[3] Comprehensive books on stereochemistry encompassing these 150 years: K. Freudenberg, *Stereochemie,* F. Deuticke, Leipzig, **1932**; E. L.

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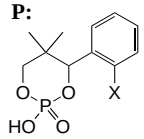
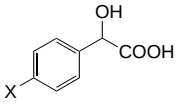
P:



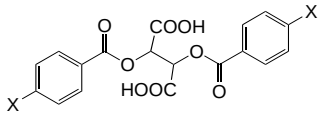
X = H, Cl, OMe

M:



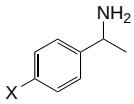
X = H, Me, Br

T:



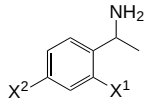
X = H, Me, OMe

Pe-I:



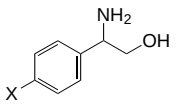
X = Cl, Br, Me

PE-II:



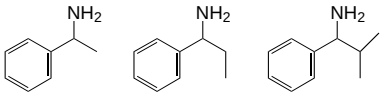
$X^1 = X^2 = H$; $X^1 = NO_2$, $X^2 = H$;
$X^1 = H$, $X^2 = NO_2$

PG:

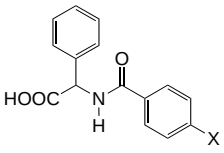


X = H, Me, OMe

PE-III:

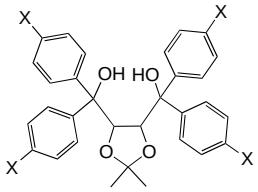


PGA:



X = H, Me, OMe

TA:



X = H, OMe

Scheme 1. Resolution of racemates with mixtures of reagents. Mixtures used: **P**: *ortho*-substituted phenylphosphoric acids; **M**: *para*-substituted mandelic acids; **T**: *para*-substituted benzoyltartrates; **PE-I**: *para*-substituted phenylethylamines; **PE-II**: nitrated phenylethylamines; **PG**: *para*-substituted 2-amino-2-phenylethanols; **PE-III**: α-alkylbenzylamines; **PGA**: *para*-substituted *N*-benzoylphenylglycines; **TA**: *para*-substituted bis(hydroxydiphenylmethyl)dioxalanes. For the preparation of the mixes, see the Experimental Section.

Eliel, *Stereochemistry of Carbon Compounds*, McGraw-Hill, New York, **1962**; J. Jacques, A. Collet, S. H. Wilen, *Enantiomers, Racemates and Resolutions*, Wiley-Interscience, New York, **1981**; E. L. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley-Interscience, New York, **1994**; the most complete description of the resolution of racemates (167 pages of chapter 7) can be found in the latter book.

[4] R. A. Sheldon, *Chirotechnology*, Marcel Dekker, New York, **1993**, chap. 6.

[5] A. D. van der Haest, H. Wynberg, *Recl. Trav. Chim. Pays-Bas* **1992** *111*, 111 – 118; A. D. van der Haest, H. Wynberg, F. J. J. Leusen, H. J. Bruins, J. H. Noordik, A. Bruggink, *Recl. Trav. Chim. Pays-Bas* **1991**, *110*, 13 – 18.

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Asymmetric Synthesis of Bryostatin 2**

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Bryostatin 1 (**1**), a biologically active marine macrolide with clinical potential for the treatment of several forms of cancer,[1] was isolated and structurally characterized by Pettit et al. in 1982.[2] Since that time, Pettit and co-workers have reported the isolation of seventeen other bryostatin macrolides, most of which differ from **1** in their substitution at C7 or C20 (e.g. **2**).[3] The biological and clinical importance of bryostatin 1 has prompted a major effort towards the syn-

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