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Survey of GMP Bulk Reactions Run in a Research Facility between 1985 and 2002

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Abstract:

A review of reactions scaled in the GMP facilities at the Pfizer-Groton site was undertaken. Reactions were categorized into one of seven categories: carbon−carbon bond formation, carboxylic acid derivative interconversion, carbon−nitrogen bond formation, carbon−oxygen bond formation, red-ox, salt formation/resolution, and other. Reactions scaled from 1997 to 2002 were compared to chemistry scaled from 1985 to 1996 to look for changes in the nature of chemistry being scaled between the two time periods. Reactions were further subcategorized within those categories, and some interesting trends were noted.

Introduction

Current synthetic methodology offers a vast array of reagents and strategies for the synthesis of potential pharmaceutical products. However, not all of these methods are practical for execution on large scale (>100 g) in a cGMP (current good manufacturing practice) setting.[1] Additionally, within the subset of methods that are potentially scaleable, experience and individual preference will usually lead to a preference for some methods over others. A recent series of discussions led us to wonder what the historical break-down would be of various reactions utilized to prepare GMP bulk in Pfizer-Groton for early clinical candidates (candidate nomination through ca. Phase 2b). The purpose of this data gathering would be severalfold, including (a) to identify preferred methods based on actual data (vs anticipated preference), (b) to identify trends over the past 15−20 years (e.g. would we see an increase in the use of transition metal-mediated cross-coupling C−C bond-forming reactions?), and (c) to see if any particular reaction classes emerge as particularly relevant to our candidate portfolio[2] and perhaps represent fruitful areas for process improvements or development of alternative methods. An anticipated benefit of this analysis is to highlight reaction classes of particular relevance to pharmaceutical R&D for the insight of academic research strategies (e.g. the dearth of hydroborations compared to the FK506 syntheses analyzed near the end of this paper were an interesting and somewhat surprising outcome of this analysis).

Another interesting question is whether the analysis of reactions scaled in our GMP facilities would differ in significant and informative ways from reactions utilized by Discovery chemists to prepare smaller quantities of potential drug candidates under non-GMP conditions. In other words, are there synthetic methods which are useful on smaller, laboratory scale to support Discovery efforts but which cannot practically be scaled to multikilogram levels? Certainly there are some reactions that fall into this category, particularly reactions that proceed through high-energy intermediates; diazotization chemistry (e.g., the Sandmeyer reaction) and aromatic nitrations are two examples that come readily to mind. While there are examples of scaling such high-energy reactions, they require significant efforts to generate the necessary supporting calorimetric and safety data prior to running the chemistry on scale.[3] Thus, alternative syntheses are frequently pursued prior to scaling such reactions.

In terms of the data presented in this paper, the vast majority of first GMP bulk campaigns utilized the Discovery synthesis with only minor modifications of solvent or specific reagent (i.e. in the majority of first campaigns, the bond-forming sequence is unchanged). Thus, the data presented here and trends noted therein reflect the Discovery chemistry utilized to prepare the candidate prior to nomination. Of course the method used in Discovery to prepare the initial 50−100 mg quantities of the candidate may have been different, as synthetic improvements are frequently made

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(1) A common misperception of Process Chemistry is that many modern synthetic methods or reagents cannot be run on scale under any circumstances; in reality, there are few reagents or methods that cannot be scaled. The more relevant questions include: can it be done safely and cost-effectively? Are there patent issues with the technology? Is the method sufficiently robust to operate reliably in a variety of facilities? Not surprisingly, there are few methods or reagents for which the answer to all of these questions is either "definitely yes" or "absolutely not." There are gray areas, and the issue is rarely "we cannot do this on any scale, an alternative must be identified", but rather "we can probably do this with the appropriate support and background work to render the process safe and robust, but there might be alternatives which will be faster and more cost-effective than optimizing the current process".

(2) Our data set was limited to Pfizer drug candidates, but given the wide variety of therapeutic areas and molecular targets pursued by Pfizer Discovery, we feel it is likely that conclusions drawn from this data set will have some relevance to pharmaceutical products as a whole.

(3) Am Ende, D. J.; DeVries, K. M.; Clifford, P. J.; Brenek, S. J. *Org. Process Res. Dev.* **1998**, *2*, 382−392.

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during the synthesis of larger, multigram quantities for further in vitro and in vivo biological testing. Analysis of such data was judged beyond the scope of this study.

Methods and Caveats

Reactions were divided into seven categories: carbon−carbon bond formation, carboxylic acid derivative interconversion, carbon−nitrogen bond formation, carbon−oxygen bond formation, reduction/oxidation (redox), salt formation/resolution, and other. Carbon−sulfur bond formation was omitted as a category as very few examples were run in the period analyzed; a likely reason for this is the compounds in the development portfolio. The categories were prioritized in the order listed above;[4] thus, a reaction that resulted in the formation of a carbon−carbon bond and a carbon−nitrogen bond was counted as a carbon−carbon bond-forming reaction only. A single-pot transformation was counted only once, even if multiple stages of a reaction were accomplished in one pot. For example, if a reductive amination was run with imine formation and reduction in one pot, the reaction was counted as a carbon−nitrogen bond-forming reaction and subcategorized as a reductive amination. If the same transformation were accomplished with the isolation of the imine and a second reaction to do the reduction, it would have been categorized as a carbon−nitrogen bond-forming reaction, subcategory imine formation for the first step, and redox, subcategory reduction of imine to amine for the second step.

Reactions were only counted once, regardless of the number of times they were run on scale. For a given candidate, if the bond-forming steps of the synthetic route changed during the development process, the reactions in both routes were tallied. The reactions run are largely affected by the structure of candidates in the portfolio; thus, the data could be skewed if a series of structurally similar compounds were all scaled in a given period of time. One could assume that, in such a case, preferred reaction chemistry developed for one candidate would be used on the structurally similar candidates, thus weighting the data toward chemistry amenable to large-scale work. Because of the effect of portfolio structure on reaction types scaled, care should be taken when making comparisons between data from different time periods. The time periods for the analysis are somewhat arbitrary and are related to a database change that made collating data for the two different time periods more straightforward.

Results and Discussion

Figure 1 graphically displays the high-level breakdown for the reactions classified. These data encompass chemistry scaled from 1985 to 2002; examination of the distribution

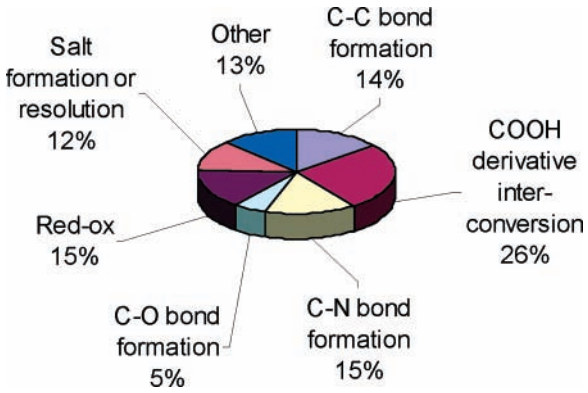

Figure 1. **Distribution of reactions surveyed.**

for 1985−1996 vs 1997−2002 shows little change for these broad reaction categories (data not shown). This is in contrast to the numerous changes seen within each reaction category for the two time periods (vide infra). This likely reflects the lack of a dramatic change in the chemical structures of candidates within these time frames, as well as the relative homogeneity of raw materials with which to work (e.g. new synthetic methods might change the *manner* in which we make C−N bonds, but the fact that you have to make the bond in the first place has not changed). The total number of reactions examined was between 2000 and 3000 for the time period 1985−2002 (note that, due to the caveats noted above in terms of not counting multiple campaigns, this does not necessarily reflect the total Pilot-Plant usage during this time period). The reactions in each category were further subcategorized to look for trends or preferences within specific transformations.

Carbon−Carbon Bond Formation. In the case of carbon−carbon bond formation, reactions were subcategorized into the reaction types listed in Table 1. The majority of carbon−carbon bond-forming reactions were anionic in nature (entry 10, the combination of entries 1−9 in the table) as opposed to cationic in nature (entry 16, the combination of entries 11−15 in the table) by a >2.5× margin. It is not clear if this is a function of the robustness of anionic vs cationic processes or a result of portfolio structure necessitating more anionic chemistry. There are a few noteworthy trends comparing the data from 1985 to 1996 to the data from 1997 to 2002. A significant increase in the use of cross-couplings in the more recent data comes at the expense of both anionic and cationic processes, highlighting the relative utility and robustness of these reactions on scale (note also the decrease in Wittig olefinations from 1.9 to 0%; a Heck cross-coupling is a potential substitute for a Wittig condensation, and could in part account for this decrease). The significant decrease in the percentage of aldol reactions utilized is likely a result of portfolio changes; a comparable decrease in the hydrogenation of aldol condensation products (vide infra) suggests that the aldol-hydrogenation sequence was not just replaced by a cross-coupling−hydrogenation sequence. There was a significant increase in the use of alkyl and aryllithium reagents (up 8.2%) despite a net decrease in the ratio of total anionic processes run in the later period, suggesting that lithium anion chemistry has gained in utility.

(4) The rationale for the rank ordering of categories was largely arbitrary. Placing carbon−carbon bond formations first reflects the widely held view that in any synthetic sequence, C−C bond formation is the central strategic element and is fundamentally more challenging than functional group interconversions. We placed carboxylic acid derivatives second in priority so that C−O and C−N bond formations would not include ester or amide bond formation, which we felt was fundamentally more straightforward than, e.g. S_NAr of an alcohol onto a bromoarene, or reductive amination of an amine and aldehyde.

Table 1. **Subclassification of carbon−carbon bond-forming reactions**

entry	reaction category	C−C bond formations 1985−2002 no. of reactions (% of total)	1985−1996 no. of reactions (% of total)	1997−2002 no. of reactions (% of total)
1	aldol	59 (17.8)	42 (20.2)	17 (13.7)
2	enolate addition to imine/nitrile	3 (0.9)	2 (1.0)	1 (0.8)
3	Claisen	46 (13.9)	31 (14.9)	15 (12.1)
4	enolate alkylation	37 (11.1)	22 (10.6)	15 (12.1)
5	Grignard addition	31 (9.3)	21 (10.1)	10 (8.1)
6	cyanide addition	8 (2.4)	7 (3.4)	1 (0.8)
7	Wittig olefination	4 (1.2)	4 (1.9)	0 (0)
8	Michael addition	24 (7.2)	14 (6.7)	10 (8.1)
9	Lithium carbanion addition	15 (4.5)	3 (1.4)	12 (9.7)
10	**total anionic C−C bond formation (entries 1−9)**	**227 (68.4)**	**146 (70.2)**	**81 (65.3)**
11	Friedel−Crafts acylation	34 (10.2)	24 (11.5)	10 (13.7)
12	Friedel−Crafts aldehyde	3 (0.9)	3 (1.4)	0 (0)
13	Friedel−Crafts alkylation	4 (1.2)	3 (1.4)	1 (0.8)
14	imminium ion addition	8 (2.4)	6 (2.9)	2 (1.6)
15	Duff reaction	14 (4.2)	10 (4.8)	4 (3.2)
16	**total cationic C−C bond formation (entries 11−15)**	**63 (19.0)**	**46 (22.1)**	**17 (13.7)**
17	cross-coupling	27 (8.1)	9 (4.3)	18 (14.5)
18	miscellaneous	15 (4.5)	7 (3.4)	8 (6.4)
19	**total**	**332 (100)**	**208 (100)**	**124 (100)**

Table 2. **Subclassification of carboxylic acid derivative interconversion reactions**

entry	reaction category	carboxylic acid interconversions 1985−2002 no. of reactions (% of total)	1985−1996 no. of reactions (% of total)	1997−2002 no. of reactions (% of total)
1	protection/deprotection	156 (25.4)	100 (24.8)	56 (26.7)
2	amide bond formation	140 (22.8)	59 (14.6)	81 (38.6)
3	ester−acid interconversion	141 (23.0)	104 (25.8)	37 (17.6)
4	other	176 (28.7)	140 (34.7)	36 (17.1)
5	**total**	**613 (100)**	**403 (100)**	**210 (100)**

This could be due to the relative ease of generating lithium carbanions selectively relative to the corresponding Grignard reagent, improved cryogenic capabilities in the bulk facilities, and/or the increased demand for metalated coupling partners to participate in cross-coupling reactions.

Carboxylic Acid Derivative Interconversions. Carboxylic acid derivative interconversions were the most common reaction subtype run on scale. These reactions were subcategorized as follows (Table 2): protection/deprotection (e.g., CBZ or BOC formation or removal, formation or removal of ester protecting groups for alcohols); amide bond formation (e.g. acid to carboxamide, or coupling of an acid with a more complex amine fragment); ester−acid interconversions (e.g., Fischer esterification, carboxylate alkylation, saponification); and other (e.g., nitrile hydrolysis, nitrile to amidate conversion, dehydration of amide to nitrile).

Carbon−Nitrogen Bond Formation. Table 3 shows the subcategories for C−N bond formation. Several trends within these data were noted. The percentage of S_N2 and addition reactions are remarkably consistent between the two time periods (entries 4 and 9, respectively). A modest decrease in S_NAr reactions (entry 5, from 16.9 to 14.9%) was countered by an increase in metal-mediated S_NAr reactions (entry 6, from 0 to 4.5%). This likely reflects the development of Pd-mediated aryl C−N bond-forming technology (e.g., Buchwald, Hartwig).

An increase in reductive aminations (entry 10, 14.6−20.1%) is noted, along with a decrease in imine formation (entry 11, 10.0−8.2%). This could reflect an increase in one-pot reductive aminations, as opposed to a stepwise process (i.e. imine formation/isolation followed by a separate reduction). Note that entry 17 in Table 6 supports this with a decrease in imine reductions (4.6−3.8%). This point should not be overemphasised, however, as the numbers are smal and imine formation/reduction was grouped together with oximes and hydrazones.

Entry 13 shows a dramatic decrease in the use of rearrangements to form C−N bonds (e.g., Beckman or Hoffman rearrangements). This is likely portfolio driven (e.g. there were several Beckman rearrangements applied to macrolides in the 1985−1996 time period as well as conversion of commercially available benzamides to the corresponding arylamine).

Entry 14 shows no change in the percentage of nitrations to form C−N bonds. This is interesting in that it may reflect the balance between two opposing forces: (a) preference to avoid potentially hazardous nitrations as a general principle and the development of new methods to facilitate this and

Table 3. **Subclassification of carbon−nitrogen bond forming reactions**

		C−N bond formations		
entry	reaction category	1985−2002 no. of reactions (% of total)	1985−1996 no. of reactions (% of total)	1997−2002 no. of reactions (% of total)
1	S_N2 reaction involving sp^3 nitrogen	46 (13.0)	31 (14.2)	15 (11.2)
2	S_N2 reaction involving sp^2 nitrogen	30 (8.5)	17 (7.8)	13 (9.7)
3	Mitsunobu reaction	7 (2.0)	4 (1.8)	3 (2.2)
4	**total S_N2 (entries 1−3)**	**83 (23.5)**	**52 (23.7)**	**31 (23.1)**
5	S_NAr	57 (16.1)	37 (16.9)	20 (14.9)
6	S_NAr, metal mediated	6 (1.7)	0 (0)	6 (4.5)
7	1,4 addition	14 (4.0)	10 (4.6)	4 (3.0)
8	glycosidation	2 (0.6)	1 (0.4)	1 (0.7)
9	**total addition reactions (entries 4−8)**	**162 (45.9)**	**100 (45.7)**	**62 (46.3)**
10	reductive amination	59 (16.7)	32 (14.6)	27 (20.1)
11	imine/oxime/hydrazone formation	33 (9.3)	22 (10.0)	11 (8.2)
13	rearrangements	10 (2.8)	10 (4.6)	0 (0)
14	nitration	13 (3.7)	8 (3.7)	5 (3.7)
15	heterocycle formation	76 (21.5)	47 (21.5)	29 (21.6)
16	**total**	**353 (100)**	**219 (100)**	**134 (100)**

Table 4. **Subclassification of carbon−oxygen bond forming reactions**

		C−O bond formations		
entry	reaction category	1985−2002 no. of reactions (% of total)	1985−1998 no. of reactions (% of total)	1997−2002 no. of reactions (% of total)
1	Mitsunobu	14 (10.9)	9 (11.8)	5 (9.6)
2	S_N2	56 (43.8)	34 (44.7)	22 (42.3)
3	S_NAr/Ullman	33 (25.8)	18 (23.7)	15 (28.8)
4	**total displacement reactions (entries 1−3)**	**103 (80.5)**	**61 (80.3)**	**42 (80.8)**
5	1,4 addition	1 (0.8)	1 (1.3)	0 (0)
6	cationic reactions (carbocation, oxonium ion)	17 (13.3)	8 (10.5)	9 (17.3)
7	hydroboration	4 (3.1)	3 (3.9)	1 (1.9)
8	oxidation	3 (2.3)	3 (3.9)	0 (0)
9	**total**	**128 (100)**	**76 (100)**	**52 (100)**

(b) the advent of technology within our process safety evaluation group to support scale-up of those nitrations which offer a significant synthetic advantage and for which the safety data gathered support safe scale-up.

Carbon−Oxygen Bond Formation. Carbon−oxygen bond formation was by far the least common bond formation scaled in our facilities, comprising less than 7% of all reactions run (Table 4). Of these, displacement reactions comprised the majority (ca. 80%). Interestingly, hydroborations decreased (entry 7, 3.9−1.9%). Given the total percentage for C−O bond-forming reactions (Figure 1, 5.0 and 6.1%), this translates to a total percentage of hydroborations of just 0.20 and 0.12% for these two time periods (contrast with S_N2 C−O bond formations of 2.2 and 2.6% for the two time periods). Thus, in contrast to the high level of academic interest in hydroboration of olefins as a C−O bond-forming method, this appears to not be a preferred method within a GMP setting.

Reductions and Oxidations. The redox category was also subcategorized, and the results are in Table 5. Reductions outnumbered oxidations by >4:1. If oxidations are considered inherently acidic in nature and reductions inherently basic, this preference for reduction over oxidation is consistent with the predominance of anionic processes in both carbon−carbon and carbon−oxygen bond formations. Other explanations for the low incidence of oxidations are the inherent safety concerns associated with oxidative processes and the disposal of hazardous byproducts. A very common question asked is "What is the preferred method for oxidizing an alcohol on scale?" Based on the data below, the answer would be that alcohols are very infrequently oxidized on scale and that alternative starting materials or sequences should be considered. MnO_2 oxidations seem to be preferred in the case of benzylic oxygen oxidation, otherwise TEMPO or Swern oxidations predominate. Dihydroxylation reactions and oxidative cleavage reactions were very seldom employed. The low incidence of oxidations involving a C−O bond is in line with the low number of carbon−oxygen bond formations and is most likely portfolio related. There was a notable decrease in reductions of carboxylic acid derivatives to alcohols in the recent data, which may be partially related to the decrease in alcohol oxidations and the slight increase in aryl ether formation relative to alkyl ether formation that is evident from the data on C−O bond formation (Table 4, entries 2 and 3). Also noteworthy is a decrease in the number of aldol condensation product hydrogenations, correlating to the decrease in aldol reactions run (Table 1, entry 1). Given the small number of oxidations run, care should be taken in drawing many conclusions from apparent trends in the data.

Table 5. **Subclassification of redox reactions**

entry	reaction category	redox reactions 1985−2002 no. of reactions (% of total)	redox reactions 1985−1996 no. of reactions (% of total)	redox reactions 1997−2002 no. of reactions (% of total)
1	MnO_2 oxidation	7 (2.0)	7 (3.2)	0 (0)
2	TEMPO oxidation	8 (2.3)	4 (1.8)	4 (3.0)
3	Swern/Moffatt oxidation	4 (1.1)	2 (0.9)	2 (1.5)
4	other alcohol oxidations (Jones, permanganate, silver nitrate)	4 (1.1)	4 (1.8)	0 (0)
5	**total alcohol oxidation (entries 1−4)**	**23 (6.6)**	**17 (7.8)**	**6 (4.5)**
6	sulfide to sulfoxide/sulfone	6 (1.7)	5 (2.3)	1 (0.8)
7	dihydroxylation (OsO_4 or RuO_4)	6 (1.7)	3 (1.4)	3 (2.2)
8	oxidative cleavage (olefin, epoxide, diol)	11 (3.1)	5 (2.3)	6 (4.5)
9	other oxidations	13 (3.7)	5 (2.3)	8 (6.0)
10	**total oxidations (entries 5−9)**	**59 (16.8)**	**35 (16.0)**	**24 (18.0)**
11	deprotection (N-debenzylation, etc.)	48 (13.7)	21 (9.6)	27 (20.3)
13	benzylic oxygen to alkane reduction	9 (2.6)	5 (2.3)	4 (3.0)
14	hydride reduction to alcohol or aldehyde	60 (17.1)	46 (21.1)	14 (10.5)
15	Wolff−Kishner reduction	5 (1.4)	5 (2.3)	0 (0)
16	dehalogenation	10 (2.8)	6 (2.8)	4 (3.0)
17	imine/oxime/hydrazone reduction to amine	15 (4.3)	10 (4.6)	5 (3.8)
18	carboxylic acid derivative reduction to amine	31 (8.8)	19 (8.7)	12 (9.0)
19	reduction of nitro or hydroxylamine to amine	55 (15.6)	32 (14.7)	23 (17.3)
20	**total reductions resulting in an amine (entries 17−19)**	**101 (28.8)**	**61 (28.0)**	**40 (30.1)**
21	aldol condensation product hydrogenation	26 (7.4)	22 (10.1)	4 (3.0)
22	other olefin hydrogenation	12 (3.4)	6 (2.8)	6 (4.5)
23	pyridine hydrogenation	14 (4.0)	9 (4.1)	5 (3.8)
24	other aryl ring hydrogenation	1 (0.3)	1 (0.4)	0 (0)
25	heteroatom−heteroatom bond cleavage	4 (1.1)	1 (0.4)	3 (2.2)
26	other reductions	1 (0.3)	0 (0)	2 (1.5)
27	**total reductions (entries 11−16, 20, 21−26)**	**292 (83.2)**	**183 (83.9)**	**109 (82.0)**
28	**total**	**353 (100)**	**219 (100)**	**134 (100)**

Table 6. **Comparison to academic syntheses**

entry	reaction category	Pfizer-Groton 1985−2002 GMP (%)	FK506 syntheses % of total (no. of reactions)	reserpine syntheses % of total (no. of reactions)
1	carbon−carbon bond formation	14.1	17.2 (60)	15.6 (15)
2	carboxylic acid derivative interconversion	26.0	10.9 (38)	28.1 (27)
3	carbon−nitrogen bond formation	15.0	0	5.2 (5)
4	carbon−oxygen bond formation	5.4	14.4 (50)	9.4 (9)
5	reduction/oxidation	14.9	28.2 (98)	35.4 (34)
6	salt formation/resolution	12.1	0.6 (2)	1.1 (1)
7	other	12.6	28.7 (100)	5.2 (5)

Comparison to Academic Syntheses. Following this analysis, we thought it would be interesting to compare these data to two natural products which have been prepared by several research groups: FK506 and reserpine. We reasoned that FK506 is representative of a typical polypropionate natural product, and reserpine, of a polycyclic alkaloid. The numbers for this analysis are contained in Table 6.

Obviously, the low number of reactions for the total syntheses compared to the Pfizer data precludes statistically significant comparison. Nevertheless, it is interesting to consider those categories where a >10% discrepancy is seen. We begin with the FK506 data, for which we analyzed three total syntheses[5] and three formal total syntheses.[6] The discrepancies are highlighted below:

- C−N bond formation (entry 3, 15 vs 0%). Clearly, this is portfolio driven: the majority of drug candidates we encounter contain nitrogen, whereas FK506 is largely polypropionate, with a single amide nitrogen derived from a commercially available amino acid.
- Reduction/oxidation (entry 5, 14.9 vs 28%). The "aldol-like" strategy for the FK506 synthesis involved numerous reduction/oxidation sequences (e.g. ester reduction to alcohol, Swern oxidation to aldehyde). This likely increases the percentage of redox reactions (and is representative of many other polypropionate syntheses).
- Salt formation/resolution (entry 6, 12.1 vs 0.6%). The two entries for the FK506 work were resolution of the pipecolinic acid side chain; nearly all subsequent intermediates were neutral compounds (or carboxylic acids not isolated

(5) (a) Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc*. **1990**, *112*, 2998−3017. (b) Nakatsuka, M.; Ragan, J. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc*. **1990**, *112*, 5583−5601. (c) Ireland, R. E.; Gleason, J. L.; Gegnas, L. D.; Highsmith, T. K. *J. Org. Chem*. **1996**, *61*, 6856−6872.

(6) (a) Jones, A. G.; Villalobos, A.; Linde, R. G., II; Danishefsky, S. J. *J. Org. Chem*. **1990**, *55*, 2786−2787. (b) Gu, R.; Sih, C. J. *Tetrahedron Lett*. **1990**, *31*, 3287−3290. (c) Smith, A. B., III; Chen, K.; Robinson, D. J.; Laakso, L. M.; Hale, K. J. *Tetrahedron Lett*. **1994**, *35*, 4271−4274.

as salts). In addition to the neutral nature of the target molecule, this reflects the standard academic bias in favor of flash chromatography, which is arguably more convenient on the modest laboratory-scale conditions being utilized (50 mg to 5 g, typically).

• Related to the previous point, in the majority of the FK506 work, chiral fragments were prepared in enantiomerically enriched form (>90% ee) and coupled in sequence to prepare the natural product. Had these fragments been readily available from commercial material, a resolution might have been competitive with the enantioselective syntheses utilized (e.g. chiral-pool starting materials such as carbohydrates, chiral auxiliaries such as those of Evans or Oppolzer, and enantioselective catalysis such as Noyori's β-ketoester hydrogenation or Sharpless epoxidation). Were this the case, the entry 6 discrepancy would be reduced.

• In the FK506 work, four of the 50 C−O bond-forming reactions were hydroborations, which represents 1.1% of the total steps (348). This is 5−10× higher than the GMP numbers for this reaction (0.12−0.20%, vide supra).

• The large value for the "other" category (28.7%) is in large part due to the many silyl ether blocking groups which were installed and removed during the course of the aldol-based methodology employed. This strategy, common with polypropionate-type structures, does not arise as frequently in alkaloid structures, such as reserpine, nor in pharmaceutical portfolios.

The reserpine analysis also yields several intriguing comparisons. Two formal total syntheses[7] (Pearlman and Wender) and three total syntheses[8] (Woodward, Martin, and Hanessian) were arbitrarily selected and the reactions totaled. The numbers for this analysis are shown in Table 6. The similarity to the GMP data is intriguing.• The fraction of C−C bond-forming reactions are almost identical. Interestingly, for reserpine almost 50% of the C−C bond formations fall into the miscellaneous category (Diels−Alder, Cope, radical), whereas only 5% of the GMP C−C bond-forming reactions are in this category.

• Carboxylic acid interconversions are almost identical. C−O bond formations are substantially similar.

• C−N bond formation is lower in the reserpine case. At first glance this appears unusual, but keep in mind that a number of the C−N bonds of reserpine are formed in a two-step sequence of amide formation/amide reduction.

• The number of redox reactions is much higher in the reserpine case. This appears to be due to the greater number of oxidations, particularly ones that we would be hesitant to use on large scale (chromium-based oxidations, olefin cleavage, epoxidations).

Conclusions

Comparing the time periods of 1985−1996 to 1997−2002, there was less than 2% change in the percentage of reactions falling into the main categories used above. Over the same time period, significant changes in the types of reactions used to form the bonds in those categories were evident. Thus, as an example, while the need to make C−C bonds has remained steady at 14% of the total portfolio, the reactions used to make those bonds have changed over the time periods. The use of anionic chemistry and reductions remained about 4 times as frequent as the use of Lewis-acidic chemistry and oxidations; however, in the case of C−C bond formation both have decreased somewhat as the use of Pd-catalyzed cross-coupling reactions has significantly increased. Also, the use of organolithium reagents appears to be reducing the use of Grignard reagents on scale. In the case of C−N bond formation, heavy metal-catalyzed couplings are reducing the use of S_NAr reactions. The low number of ketone reductions, dihydroxylations, epoxidations relative to other more modern catalytic methods such as the number of Pd-catalyzed cross-couplings used may be evidence that the generally proprietary nature of these methods renders the purchase of stereocenters from natural sources or the resolution of racemic mixtures more cost-effective.

The data presented above demonstrate that, while there are methodologies that are preferred on large scale, almost any type of reaction can be and was scaled. Chemistry that is covered by patents, including many of the newer catalytic methods in the literature, is generally avoided. A review of the candidates that were analyzed in this study revealed that in almost every case the initial discovery chemistry was scaled at least once, and thus the data presented include those discovery routes in addition to the process routes that replaced them.

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