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Lecture Transcripts

The Story of Lescol: From Research to Production†

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Abstract:

Process R&D transformed a research synthesis of fluvastatin into a commercial process. The major hurdle in the synthesis was the stereoselectivity of the *syn*-diol formation. The problem was attacked and solved from three directions. First, a method was developed that separated the *syn* and *anti* isomers that did not require chromatography. Second, a new, totally stereoselective synthesis, starting with phloroglucinol, was designed to produce the side-chain containing the *syn*-diol. And third, a new and general stereoselective reaction was invented for the reduction of *β*-hydroxy ketones to *syn*-diols. The 99% *syn*-selectivity of this reaction was achieved with sodium borohydride as the reducing agent, diethylmethoxyboron as the chelating agent, and tetrahydrofuran and methanol as solvents in a 4:1 ratio, at −70 °C. The final process was only six steps long, entirely stereoselective in both the *E*-olefin and *syn*-diol formation, and required no chromatography. The cost of the synthesis was thus reduced by a factor of 14.

I. Introduction

In the seventies it became clear that a high serum-cholesterol level is a risk factor for atherosclerosis and other cardiovascular diseases and that diet alone may not lower the cholesterol sufficiently. Our bodies produce more cholesterol than we ingest; thus, if one is genetically predisposed, high levels of cholesterol will persist even with careful diet. A better approach then is to block the biosynthesis of cholesterol by a drug. Several pharmaceutical companies saw this as an unmet medical need and embarked on the search for an inhibitor of cholesterol biosynthesis. The pathway of the biosynthesis of cholesterol was well-known at the time, so that one could choose from several steps and several enzymes which to inhibit. Some work was done with squalene synthetase, but most success[1] came with HMG-CoA reductase, the enzyme that reduces 3-hydroxy-3-methylglutaric acid to mevalonic acid. Most statins resemble mevalonic acid in the sense that they contain the 3,5-dihydroxy carboxylate function; this fools the enzyme into binding with the drug, and it thus becomes disabled.

Novartis' contribution to this field was Lescol (fluvastatin sodium) **34**. What are the challenges in synthesizing this molecule? First, we have to synthesize the indole portion, second, we have to prepare the olefin in the E-configuration; and third and most difficult, we have to form the 3,5-diol exclusively in the *syn*-configuration. The molecule is racemic, and therefore we do not have to address the issue of absolute stereochemistry at this time.

The function of Process R&D is to translate a research synthesis into a plant process. The difference is not just a matter of scale but also a matter of quality. An ideal process should have the following qualities: it should be safe, ecologically sound, economical, reproducible, it must fit the plant physically, and the drug substance must meet predetermined quality specifications. Let's review the medicinal chemist's synthesis, which is usually our starting point. When we received this project, the structure of the drug substance (**11**) was somewhat different: an *N*-methyl instead of the *N*-isopropyl group and a lactone instead of the open dihydroxycarboxylate side chain. We will switch to the correct structure as we develop the synthesis.

II. The Research Synthesis

The research chemist[2,3] prepared (Scheme 1) the indole by a Fischer indole synthesis. Thus *p*-fluorobenzyl bromide (**1**) was substituted with ethyl acetoacetate, and the ketone **2** was condensed with phenyl diazonium (**3**). A cyclization with loss of ammonia produced the indole **4**. The nitrogen was methylated with methyl iodide, and the ester **5** was reduced with diisobutylaluminum hydride to give the primary alcohol **6**, which was back-oxidized to the aldehyde **7** with manganese dioxide in diethyl ether. The side chain was extended by two carbon atoms with tri-*n*-butylstannylvinyl ethoxide and *n*-butyllithium as the transmetallating agent, to give the conjugated aldehyde **8**. The side chain was further extended by four carbon atoms with methyl acetoacetate, and the resulting ketone **9** was reduced with borane to give diol **10**. The ester was saponified, acidified, and heated to form lactone **11**, which was the drug substance at the time. The reduction of the ketone **9** was not stereoselective, so that

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(1) Kathawala, F. G. *Med. Res. Rev.* **1991**, *11*, 121.

(2) Kathawala, F. G. U.S. Patent 5,354,772, 1994.

(3) Kathawala, F. G. U.S. Patent 4,739,073, 1988.

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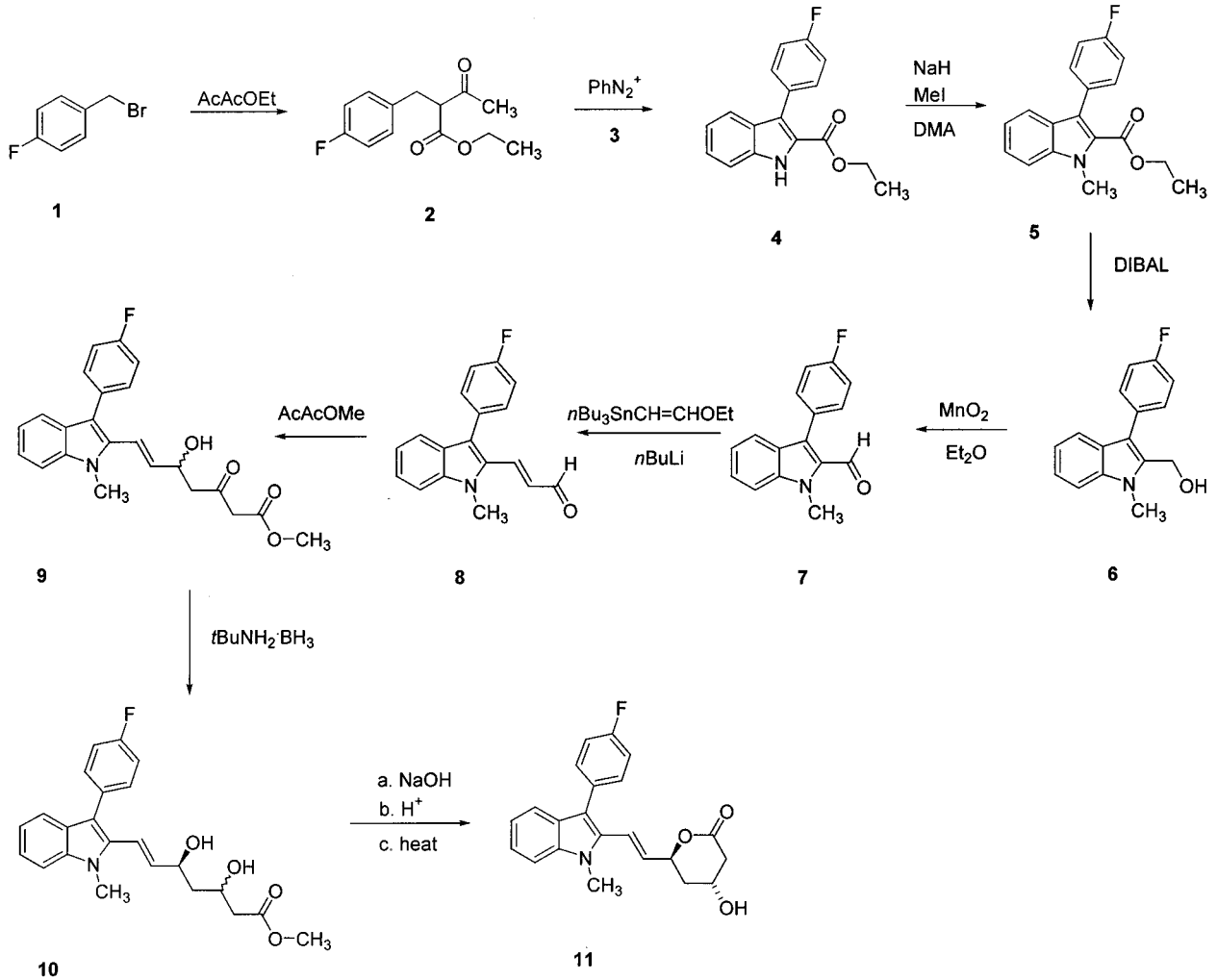
Scheme 1

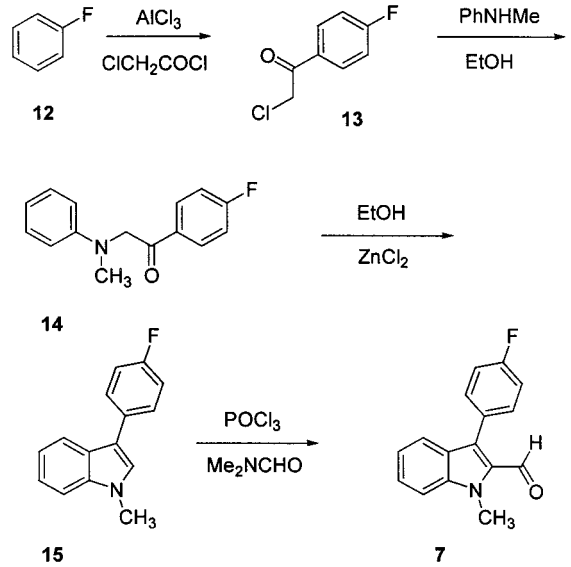


the *cis*- and *trans*-lactones had to be separated. This required a difficult chromatography (poor resolution) and several crystallizations, and the yield of this step was only 15%!

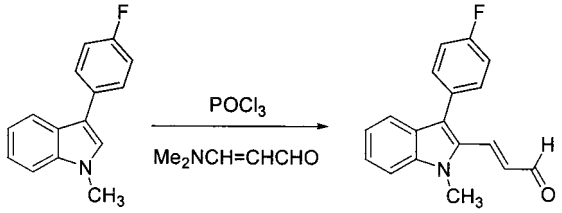
Keeping the criteria of an ideal process in mind, let us analyze this synthesis. We notice the following potential problems that will have to be by-passed with process development: (*i*) the starting material, *p*-fluorobenzyl bromide, was expensive and unavailable in bulk quantities (economy); (*ii*) several intermediates, reagents or solvents (diazonium salt, methyl iodide, diethyl ether) are unacceptable on a plant scale (safety); (*iii*) manganese dioxide is undesirable (ecology); (*iv*) tri-*n*-butylstannylvinyl ethoxide is toxic, not available in bulk quantities, and is difficult to prepare (economy, safety, ecology); (*v*) the reduction is not stereoselective so that chromatography and several crystallizations were needed (economy, ecology, plant fit, specifications); (*vi*) last but not least, the synthesis is relatively long at 11 steps.

Since we were faced with so many potential problems in a synthesis, the best strategy was to design a new synthesis. We did this by switching from the Fischer to the Bischler indole synthesis (Scheme 2). Thus, fluorobenzene (**12**) was acylated in the *p*-position with chloroacetyl chloride, and the chlorine was substituted with *N*-methylaniline. The resulting ketone **14** was cyclized with zinc dichloride in ethanol to give indole **15**. This indole admittedly has no substituent in the 2-position, and there was no precedent in the literature for formylating indoles in the 2-position, and thus, we invented this reaction.[4] On treatment with *N*,*N*-dimethylformamide and phosphorus oxychloride, indole **15** is formylated

Scheme 2

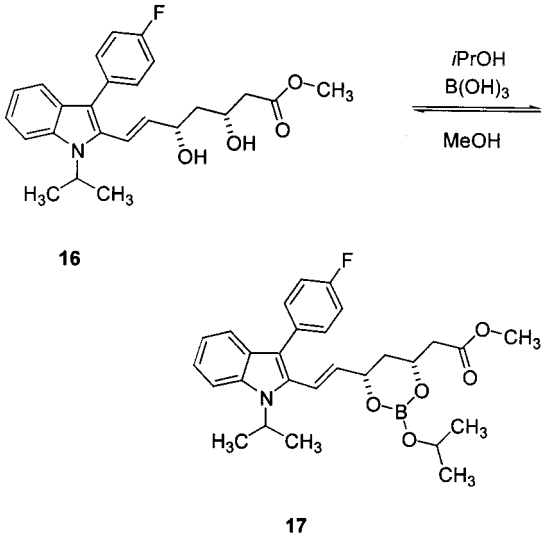


Scheme 3



15 8

Scheme 4



16 17

Table 1. **Purification by recrystallization of the borate derivative**

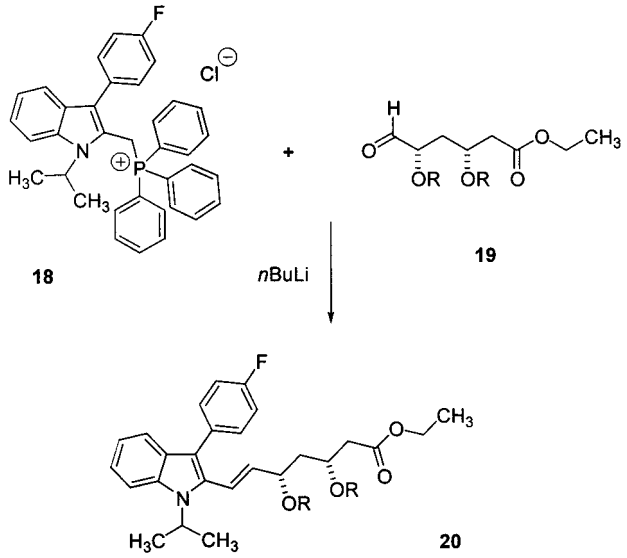
recrystallization number	*syn*	*anti*
0	60	40
1	75	25
2	89	11
3	94	6
4	97	3
5	98	2

to obtain **7** in good yield. When the medicinal chemists were informed of this reaction, they extended the idea to the three-carbon analogue (Scheme 3). If, instead of *N*,*N*-dimethylformamide, one uses *N*,*N*-dimethyl-3-aminoacrolein, one can obtain the conjugated aldehyde **8** directly. This new strategy not only shortened the synthesis by one step but also eliminated all undesirable parameters *i*−*iv* listed above! The only major hurdle remaining then was the nonstereoselective reduction of the β-hydroxyketone.

We attacked and solved this problem from three independent directions, more or less in parallel. First, we developed a method for separating the isomers without the use of chromatography. Second, we designed a new, totally stereoselective synthesis of fluvastatin. And third, we optimized the stereoselectivity of the reduction of the β-hydroxy ketone until it was 99% *syn*. Having given away the punch line, let me describe these three solutions in turn.

(4) Walkup, R. E.; Linder, J. *Tetrahedron Lett.* **1985**, *26*, 2155.

Scheme 5



18 19 20

II. Separation of Isomers

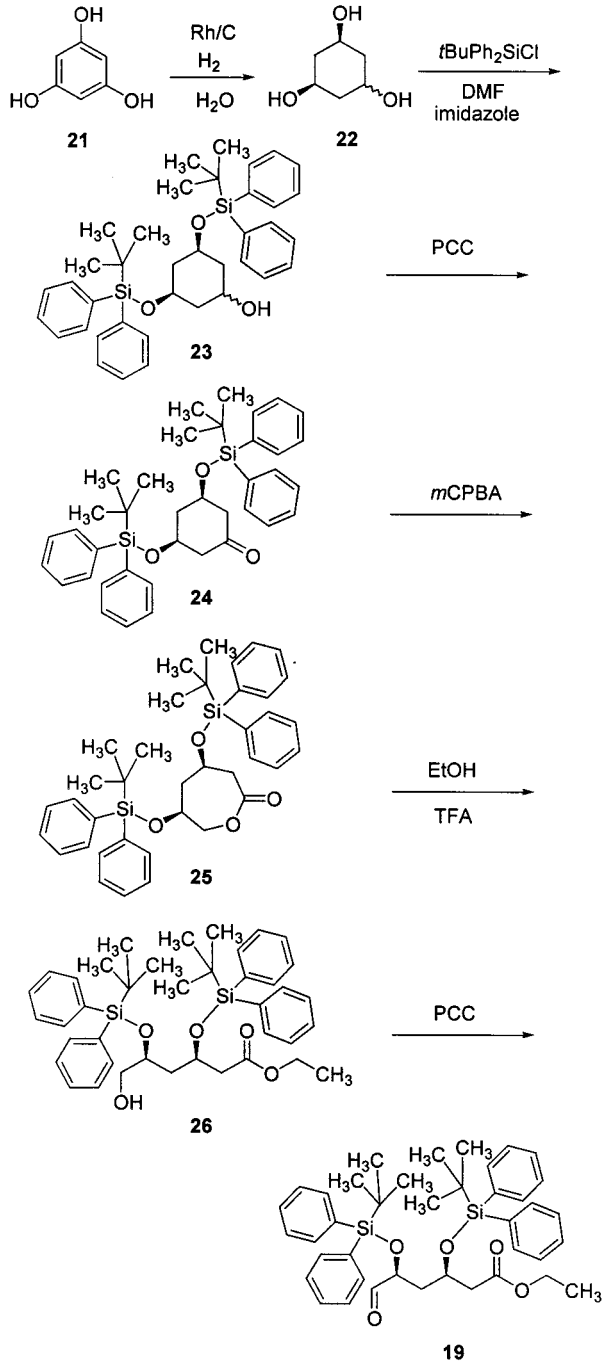
First, we designed a method for separating the isomers without the need for chromatography. It is reported in the literature[5] that 1,3-diols form borates with boric acid. Indeed, our diol **16** also formed a cyclic borate **17** with boric acid in 2-propanol (Scheme 4). The isopropyl group in **17** was introduced by the solvent, but more importantly, borate **17** was crystalline, and each crystallization removed half of the unwanted *anti*-isomer. Thus, starting with a 60:40 mixture of *syn*- and *anti*-isomers, it required five crystallizations to obtain >98% pure product (Table 1). The boron could then be removed with methanol; the resulting methyl borate forms an azeotrope[6] with methanol and can be removed by distilling off the methanol in several portions. This method was actually used in the early phases of development and is a good example of how one has to compromise in process development: we sacrificed yield and cost (which were poor) for the sake of safety, plant fit, specifications, and reproducibility (which were excellent). In other words, the plant can easily perform crystallizations, and we obtained the pure product in this manner. However, for the long run, the procedure was too expensive, since the yield of this step was still only 35% (but already twice that of the research synthesis!). For these reasons, we pursued a second approach, a new, totally stereoselective synthesis of fluvastatin.[7]

III. A New Stereoselective Synthesis

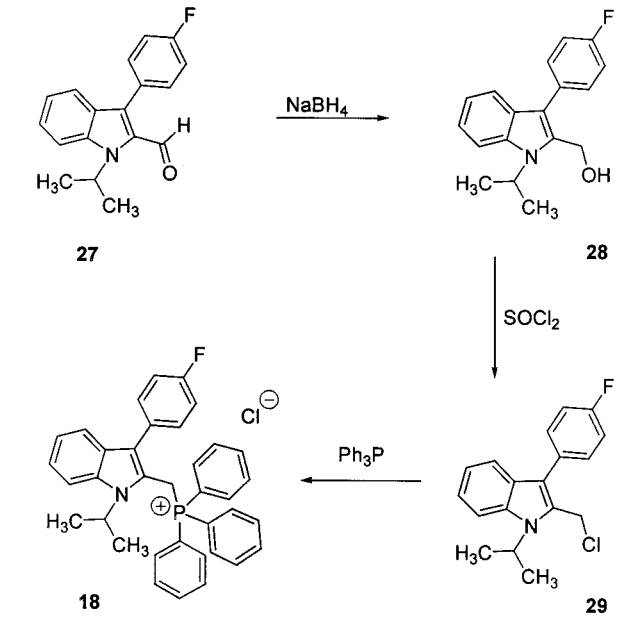
Thus far we have seen the side chain built by a formylation and two-carbon chain extension (**15**→**7**→**8**), or by a direct vinylogous formylation (**15**→**8**). There is a third possibility, which is to attach a six-carbon side chain **19** directly to form the olefin by a Wittig reaction (Scheme 5). The stereochemical problems are then shifted and focused in this side chain synthon **19**. How can one synthesize this aldehyde with the diol exclusively in the *syn*-configuration?

(5) Dale, J. *J. Chem. Soc.* **1961**, 910.
(6) Horsley, L. H. *Adv. Chem.* **1973**, *116*.
(7) Prasad, K.; Repič, O. *Tetrahedron Lett.* **1984**, *25*, 2435.

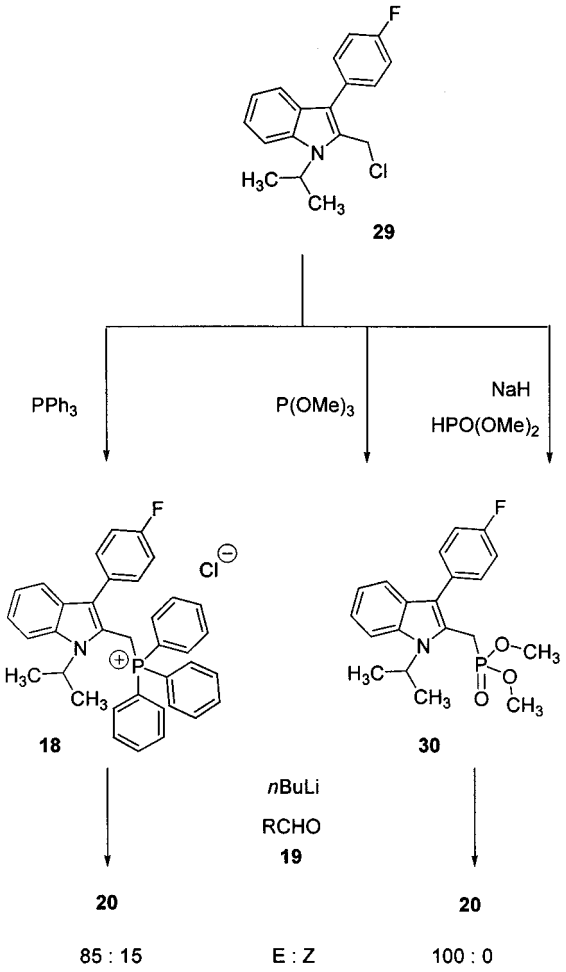
Scheme 6



Scheme 7

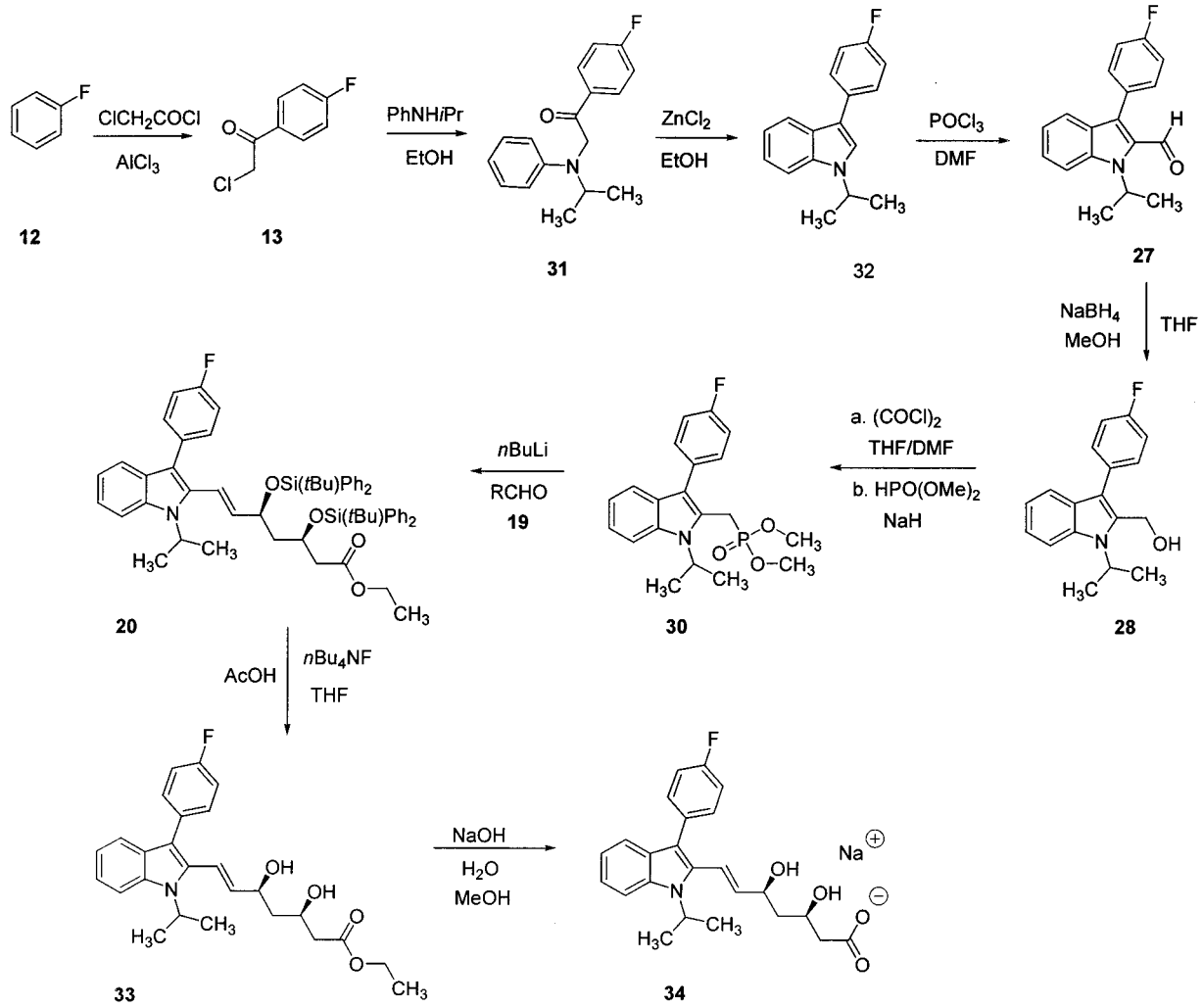


Scheme 8



Since stereochemistry is more easily defined in a cyclic molecule rather than in a floppy open chain, we used this strategy (Scheme 6). Our cyclic starting material was phloroglucinol (**21**). It can be hydrogenated with rhodium on carbon to give a mixture of *cic,cis*- and *cis,trans*-cyclohexane triols (**22**). At first we separated these two isomers by crystallization as we thought we needed pure *cis,-cis*-isomer to obtain exclusively the *cis*-diprotected triol **23**. It turns out, however, that the *trans*-hydroxy group is axial and, therefore, more hindered, and it reacts much more slowly with *tert*-butyldiphenylsilyl chloride. Thus, even a mixture of *cis,cis*- and *cis,trans*-triols gives only the *cis*-diprotected triol **23** with 2 equiv of *tert*-butyldiphenylsilyl chloride. The stereochemistry of the third hydroxyl group does not matter anyway as in the next step it is oxidized with pyridinium chlorochromate to give the ketone **24**, and further with *m*-chloroperbenzoic acid, in a Baeyer−Villiger reaction, to give[8] the seven-membered lactone **25**. Now it should be clear where we are headed, as all the atoms are in

Scheme 9



place. We opened the lactone with ethanol to obtain the ester **26** and oxidized the primary alcohol, again with pyridinium chlorochromate, to obtain the desired aldehyde synthon **19**. Note how the *cis*-diol in the cyclohexane **23** became the *syn*-diol in the open chain synthon **19**. A word about the bulky protecting groups. It is known that α-hydroxyl aldehydes readily hydrate. Water would, of course, ruin the next step, the Wittig reaction. By placing the bulky protecting groups on the hydroxyls, the hydration was entirely prevented. We believe the reason is not steric since the synthon reacts readily in the Wittig reaction after all; rather, the effect is hydrophobic: the bulky protecting groups entirely envelop the aldehyde and prevent water from reaching it.

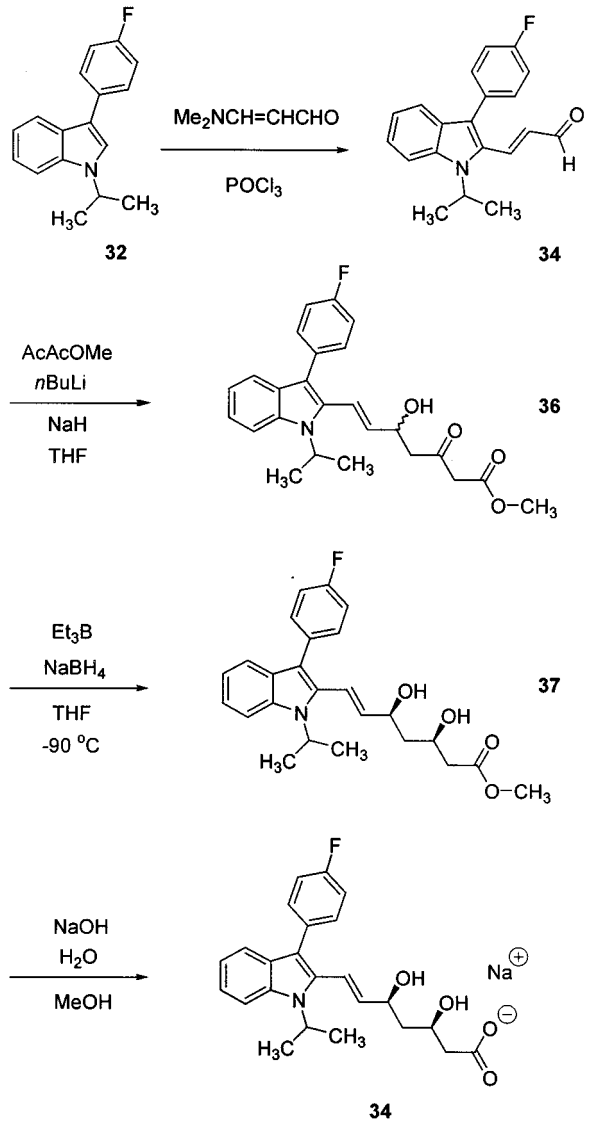
We were now ready to couple the side chain to the indole, which had to be functionalized appropriately (Scheme 7). 2-Formylindole **27** was reduced with sodium borohydride to the primary alcohol **28**, which was chlorinated with thionyl chloride, and the chloride **29** was substituted with triphenylphosphine to obtain the phosphonium chloride **18**. It was coupled in a Wittig reaction with the aldehyde synthon **19** to give olefin **20** (Scheme 8), alas with an E/Z ratio of 85:15. This was disappointing and not acceptable since the separation of isomers would again require chromatography.

(8) Prasad, K. U.S. Patent 4,841,071, 1989.

The stereochemical problem was quickly fixed by switching from the Wittig conditions to the Horner-Emmons reaction. This required the phosphonate **30**, which could be obtained from the same chloride **29** by substitution with trimethyl phosphite (Arbuzov reaction). Now phosphonate **30** reacted with the aldehyde **19** to give exclusively the *E*-olefin. This solved the selectivity problem but introduced another issue: the by-product of the Arbuzov reaction is chloromethane, a toxic compound. This safety and ecology problem was solved by switching the reagent again, this time to sodium dimethoxyphosphonate. It displaces chloride **29** to give the same phosphonate **30**, but now the only by-product is sodium chloride.

The new synthesis is summarized in Scheme 9. We refer to it as the convergent synthesis since it combines two large pieces near the end of the synthesis. It is entirely stereoselective in both the *E*-olefin and the *syn*-diol formation, so that in this sense the goal of this process research was reached. However, this synthesis was too long and too expensive. We needed 2 equiv of the heavy protecting group *tert*-butyldiphenylsilyl chloride, and by definition, the protecting groups are thrown away, adding to the cost. Also, several unacceptable oxidizing agents were used in the synthesis. For these reasons, we sought yet another solution.

Scheme 10



However, this synthesis has been used to make many analogues[9] of fluvastatin as the convergent nature of the synthesis made it convenient to attach the side chain to other heterocycles.

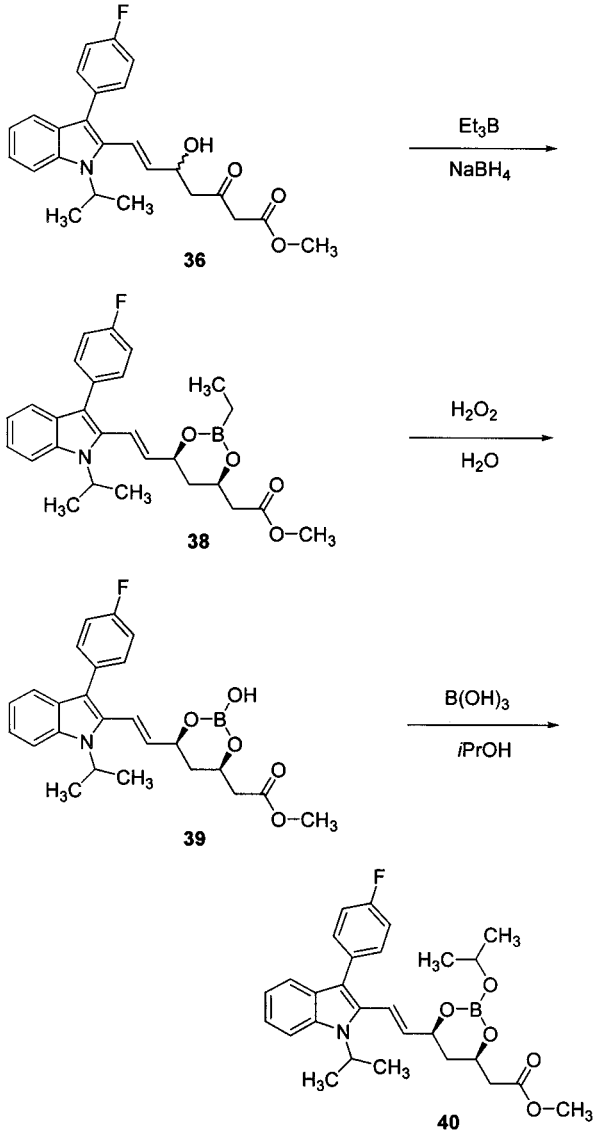
IV. Optimization of the Reduction

We returned to the linear synthesis (Scheme 10) and optimized the stereoselectivity of the reduction[10] of the β-hydroxyketone **36** to the *syn*-diol **37**. As is usual in optimizations, we varied the critical variables (in this case the reducing agent, the chelating agent, the solvent and the temperature) and observed a critical outcome (in this case the *syn/anti* ratio) shown in Table 2. This table is only an excerpt of a much larger table, just to illustrate the point. In reality, over 100 experiments were performed. For the longest time, we could not break through the barrier of the 80:20 ratio. The best conditions found in the literature were zinc borohydride[11] as both the reducing and chelating agent or sodium borohydride/triethylboron[12] as the reducing and chelating agents, respectively. These could not be used on a large scale, however, for the following reasons. Zinc borohydride is not available commercially, it is difficult to prepare and requires diethyl ether for both its formation and the reaction, which is only 76% stereoselective. The triethylboron could not be used because it is toxic and pyrophoric, the

Table 2. **Optimization of the stereoselectivity**

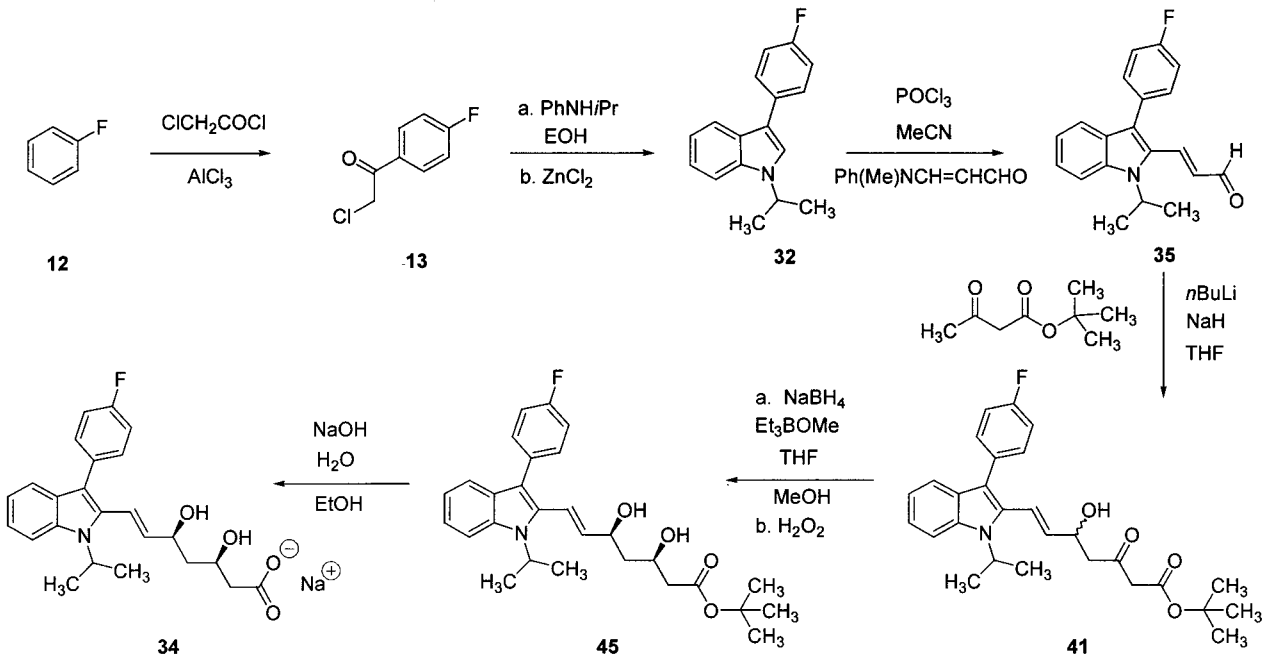
reducing agent	chelating agent	solvent	temp [°C]	*syn*	*anti*
$LiBH_4$	$Mg(O_2CCF_3)_2$	Et_2O	−78	68	32
H_2	Pt/C	EtOH	+20	64	36
$Me_2NH{\cdot}BH_3$	$Mg(O_2CCF_3)_2$	Et_2O	−78	41	59
$Zn(BH_4)_2$	$Zn(BH_4)_2$	Et_2O	−20	76	24
$NaBH_4$	Et_3B/air	THF	−78	80	20
L-Selectride	sBu_3B+HCO_2H	THF	−78	84	16
$NaBH_4$	Et_3B+MeOH	THF	−78	98	2

Scheme 11



(9) Prasad K. U.S. Patent 4,571,428, 1986.
(10) Kathawala, F. G.; Prager, B.; Prasad, K.; Repič, O.; Shapiro, M. J.; Stabler, R. S.; Widler, L. *Helv. Chim. Acta* **1986**, *69*, 803.
(11) Nakata, T.; Tani, Y.; Hatozaki, M.; Oishi, T. *Chem. Pharm. Bull.* **1984**, *32*, 1411.
(12) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233.

Scheme 12



stereoselectivity is only 80% even at low temperature (−90 °C), and it requires long reaction times (15 h). Furthermore, it requires activation with air, and the literature is vague regarding the quantity and function of this air. In any case, it seems hazardous to introduce air into a pyrophoric reagent. There was another problem with triethylboron. In the past, the borates could be cleanly removed with methanol, and the boron residues in the product were very low (5 ppm). When using triethylboron, the boron residue was stuck at about 100 ppm, even after several azeotropic distillations with methanol. We postulated that the reason for this was boronate **38**, an intermediate in this reduction (Scheme 11). Such a boronate methanolizes much more slowly than borates, so that it remained and caused the high boron residue. For this reason, we added an oxidation to the workup: hydrogen peroxide oxidizes any boronate **38** to borate **39**, which can then be recrystallized as **40** to obtain pure *syn*-diol **37**.

In any case, we persevered in the optimization, and when we added formic acid to the tri-*s*-butylboron/L-Selectride combination, for the first time we broke through the 80% selectivity. And finally, when we added methanol to the triethylboron/sodium borohydride reaction, the selectivity jumped to 98% (Table 2). What was going on? Clearly methanol reacted with triethyl boron; however, it was not clear what the active reagent was. To answer this question, we prepared or obtained all possible reagents, formally substituting one, two, and three ethyl groups with methoxyl groups, and subjected them to the same reaction conditions (Table 3). Lo and behold, it is the diethylmethoxyboron[13−15] that gives the best stereoselectivity of 99%. Our original in situ preparation of this reagent[16] with methanol gave slightly worse results than the preformed reagent as it produced other combinations of methanol and triethylboron that are less selective. The high selectivity can be explained by the mechanism of the reduction. Alcohol **36** displaces the methoxyl in diethylmethoxyboron, forming a covalent bond and allowing boron to chelate the ketone intramolecularly. This not only activates the ketone for reduction by borohydride but also forms a six-membered ring with two faces, a more-hindered and a less-hindered face, and the reduction occurs from the side of the hydrogen, resulting in the *syn*-diol. The reaction is somewhat catalytic, as the methanol in the reaction can displace the boron reagent, regenerating the diethylmethoxyboron, which can activate another molecule. The catalysis depends on the fact that, at this low temperature, the unchelated ketone does not reduce. However, the catalysis only works down to about 0.5 equiv; at lower levels of diethylmethoxyboron, the stereoselectivity deteriorates. In any case, methanol is necessary, but we optimized also the

Table 3. **Identification of the best chelating agent**

chelating agent	*syn*	*anti*
Et_3B	98	2
Et_2BOMe	99	1
$EtB(OMe)_2$	50	50
$B(OMe)_3$	35	65

Table 4. **Optimization of the solvent**

solvents	*syn*	*anti*
THF/MeOH	98.4	1.6
EtOAc/MeOH	92.7	7.3
*t*BuOMe/MeOH	91.7	8.3
PhMe/MeOH	90	10

(13) Prasad, K.; Chen, K.-M. U.S. Patent 5,189,164, 1993.
(14) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repič, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.
(15) Köster, R.; Fenzl, W.; Seidel, G. *Liebigs Ann. Chem.* **1975**, 352.
(16) Chen, K.-M.; Gunderson, K. G.; Hardtmanan, G. E.; Prasad, K.; Repič, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923.

Table 5. **Optimization of the solvent ratio**

THF:MeOH	*syn*	*anti*
20:1	94	6
10:1	96	4
6:1	97.5	2.5
4:1	98	2
3:1	97.6	2.4

Table 6. **Process R&D saves money**

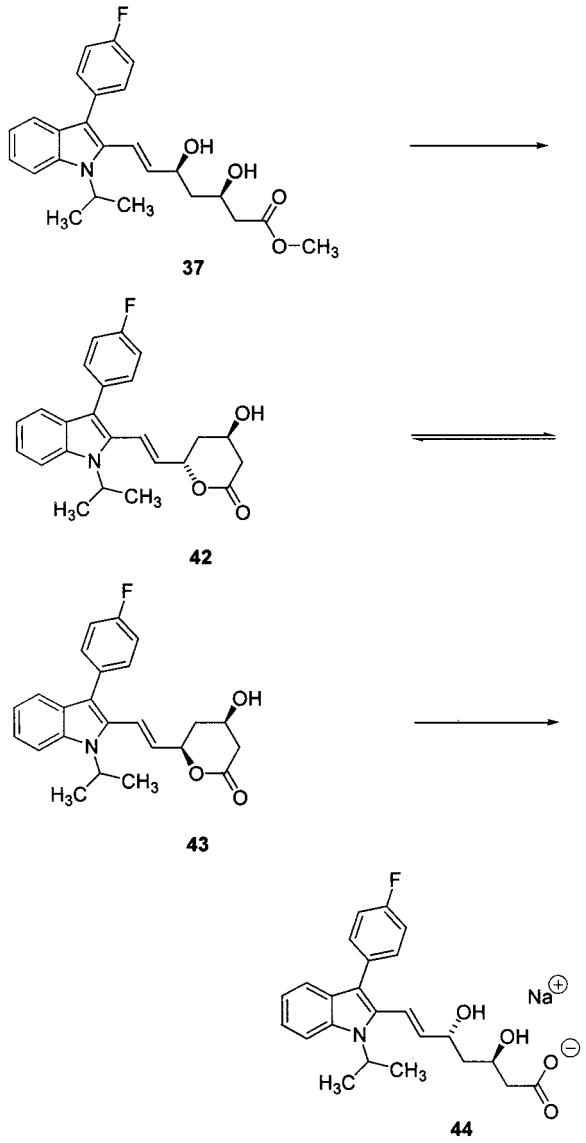
process no.	relative cost
1	14
2	39
3	7.5
4	1.5
5	1

cosolvent—the best results are in tetrahydrofuran (Table 4), and the solvent ratio—the best results are 4:1 tetrahydrofuran/methanol (Table 5). This reagent also explains the role of air in the litarature procedure. Air probably oxidizes triethylboron to diethylethoxyboron, but not as cleanly (under- or overoxidation), so that the selectivity is better with our preformed reagent.

V. Final Process

With this breakthrough in hand, we had reached the final commercial process[17] (Scheme 12). Along the way, we made several other improvements. For example, in the Bischler indole synthesis, the alkylation and cyclization steps were combined (**13**→**32**) as both were performed in ethanol, saving one step. In the vinylogous formylation of **32**, the reagent *N*,*N*-dimethyl-3-aminoacrolein was replaced with *N*-methyl-*N*-phenyl-3-aminoacrolein.[18,19] The advantages of this reagent are the following: it is easier to prepare, it requires a shorter reaction time for the formylation, and it gives a cleaner product **35**, in higher yield, with no chromatography required.[20,21] In the next step, methyl acetoacetate was replaced with *tert*-butyl acetoacetate. The main advantage is that the *tert*-butyl ester does not form lactones. This was a problem with the methyl (**37**) and ethyl ester (**33**), which lactonize readily, and moreover, the lactone **42** epimerizes in the allylic position and appears as the *anti*-diol **44** after saponification (Scheme 13). Although this isomerization occurred only to the extent of a few percent, it is unacceptable, considering how much effort we spent obtaining the pure *syn*-isomer. The *tert*-butyl ester entirely prevents the lactonization and isomerization. The *tert*-butyl acetoacetate contributes several other benefits: it brings a higher yield in the condensation (73%), it allows a higher stereoselectivity in the reduction (this was the first time we observed 99% *syn*-selectivity), and the product **45** is crystalline. One

Scheme 13



crystallization purifies it, and there is no longer any need for borate derivatization or for boron-removal operations, for example, distillation with methanol.

The process then continues (Scheme 12) with our original stereoselective reduction[14] of the β-hydroxyketone **41** with sodium borohydride as the reducing agent, diethylmethoxyboron as the chelating agent, in tetrahydrofuran/methanol (4:1) at −70 °C, to give 99% pure *syn*-diol **45**. The purity of this precursor is important as only minimal purification occurs in the last step. The saponification leaves product **34** in the aqueous layer, which is freeze-dried, to obtain the drug substance as a white powder. The hydrolysis of the *tert*-butyl ester is surprisingly fast; this is due to the acid catalysis provided by the 3- and 5-hydroxyls. We have shown that removing one or both of the hydroxyl groups progressively slows down the saponification.

This completes the process for fluvastatin (**34**). The synthesis is only six steps long, entirely stereoselective in the *E*-olefin and *syn*-diol formation, and it requires no chromatography. Considering the relative complexity of the molecule, this was quite an accomplishment.

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(18) British Patent 945,536, 1968.
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The contribution of process development is most dramatic when calculating process costs. Our final process was 14 times less expensive than the original medicinal chemist's synthesis (Table 6). The second process, the convergent route, was more expensive; the third process, utilizing the borate crystallization, doubled the yield and thus halved the cost. The fourth process incorporated the invention of the stereoselective reduction of β-hydroxyketone and cut the cost by a factor of 5, and final optimizations (combining two steps, utilizing *N*-methyl-*N*-phenyl-3-aminoacrolein, and switching to *tert*-butyl acetoacetate) cut the cost by another third. A factor of 10 to 20 in cost reduction is a common and not unusual contribution of Process R&D.

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