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An Improved Manufacturing Process for Fluvastatin

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Abstract:

An improved manufacturing process for fluvastatin 1 has been developed by performing the condensation reaction of *E*-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-2-propenal, 4, with the dianion of *tert*-butyl acetoacetate and the subsequent low-temperature reduction to 7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid-1,1-dimethylethylester, 2, without isolation of the intermediate 7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-5-hydroxy-3-oxo-6-heptenoic acid-1,1-dimethylethylester, 3. To be successful, a crucial selectivity problem in the conversion of aldehyde 4 to aldol 3 had to be understood and solved. The improved process allows the omission of two solvents, and the manufacture of fluvastatin at considerably lower cost and in higher throughput.

1. Introduction

Statins, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, have become the most frequently prescribed agent for the treatment of hypercholesterolemia because of the compelling evidence of their effect on reducing the rates of cardiovascular events.[1,2] Fluvastatin (Lescol) **1** belongs to this class of medications. It consistly lowers low-density lipoprotein cholesterol levels by 20−30% at a daily dose of 20−40 mg.[3] Lescol was first introduced in 1994 in the United Kingdom and is now available in over 80 countries. Lescol, marketed as racemic mixture, is very well tolerated and to date has not shown any clinical interactions with other commonly used drugs. This feature becomes particularly important in elderly patients who take many drugs and are susceptible to suffering from side effects related to drug interactions. Recent studies with Lescol are no longer concentrating only on blood cholesterol concentration, but have been looking into further-reaching effects such as the atherosclerotic disease process and clinical events. It has been found that Lescol slows the progressive hardening of the arteries and markedly reduces the incidence of heart attacks and other clinical events related to cardiovascular disease.

2. The Current Production Process

The transformation of the research synthesis into a highly productive production process has been described in detail[4] and is outlined in Scheme 1. It starts with an aldol-type condensation in which a solution of the now commercially available *E*-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-2-propenal, **4**,[5] in THF is added to the preformed sodium-lithium salt of *tert*-butyl acetoacetate **5** at room temperature in THF. After the usual work-up procedure, compound **3** is obtained in pure form by crystallization from a mixture of 2-propanol and heptane. During the development of the reduction of **3** to **2,** a major breakthrough occurred when it was found that the required high syn stereoselectivity in the racemic compound **2** could be achieved when the reaction was run in the presence of diethylmethoxyborane at −78 °C in THF/MeOH.[6,7] Under optimal conditions, the syn:anti ratio can be increased up to >98:2.[8] The alkaline hydrolysis of diol **2** and the isolation of fluvastatin, **1**, via freeze drying complete the manufacturing process.

The procedure as outlined in Scheme 1 is straightforward and efficient. However, in view of the increasing demand for fluvastatin, we felt a need for further improvements, in particular with regard to increasing the throughput,[9] reducing the number of solvents,[10] and improving the overall yield for the conversion **4** → **3** → **2**.

When analyzing the process for potential improvements, we came to the conclusion that omission of crystallization and drying of aldol **3** would offer the largest saving potential. Such an approach requires quantitative conversion and high selectivity for the condensation reaction **4** → **3** and, in particular, the minimization of the formation of a by-product; the reduced form of aldehyde **4**, alcohol **7** (Figure 1). Under the reaction conditions of the current process, this by-product could always be detected in the crude reaction mixture to some extent. However, since it is easily removed by crystallization, the formation of small amounts of **7** does not

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(1) Switzer, J. A.; Hess, D. C. Statins in stroke: prevention, protection and recovery. *Expert Rev. Neurother.* **2006**, *6* (2), 195.

(2) Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S), *Lancet* **1994**, *344*, 1383.

(3) Davidson, MH. Fluvastatin long-term extension trial (FLUENT): Summary of efficacy and safety. *Am. J. Med.* **1994**, *96*, 41.

(4) Repič, O.; Prasad, K.; Lee, G. T. The Story of Lescol: From Research to Production. *Org. Process Res. Dev.* **2001**, *5*, 519.

(5) Synthon Chiragenics Corporation, 7 Deer Park drive, Monmouth Junction, NJ, 08852, U.S.A. For the preparation of **4**, see: Lee, G.T.; Amedio, J. C.; Underwood, R.; Prasad, K.; Repič, O. *J. Org. Chem.* **1992**, *57*, 3250.

(6) Prasad, K.; Chen, K.-M. U.S. Patent 5,189,164.

(7) Chen, K-M.; Hardtmann, G. E.; Prasad, K.; Repič, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155.

(8) See ref 23.

(9) The production tonnage for fluvastatin is >50 tons per year.

(10) For the two steps **4** → **3** → **2** of the current process, a total of six solvents (THF, hexane, isopropanol, heptane, methanol, ethyl acetate) were used.

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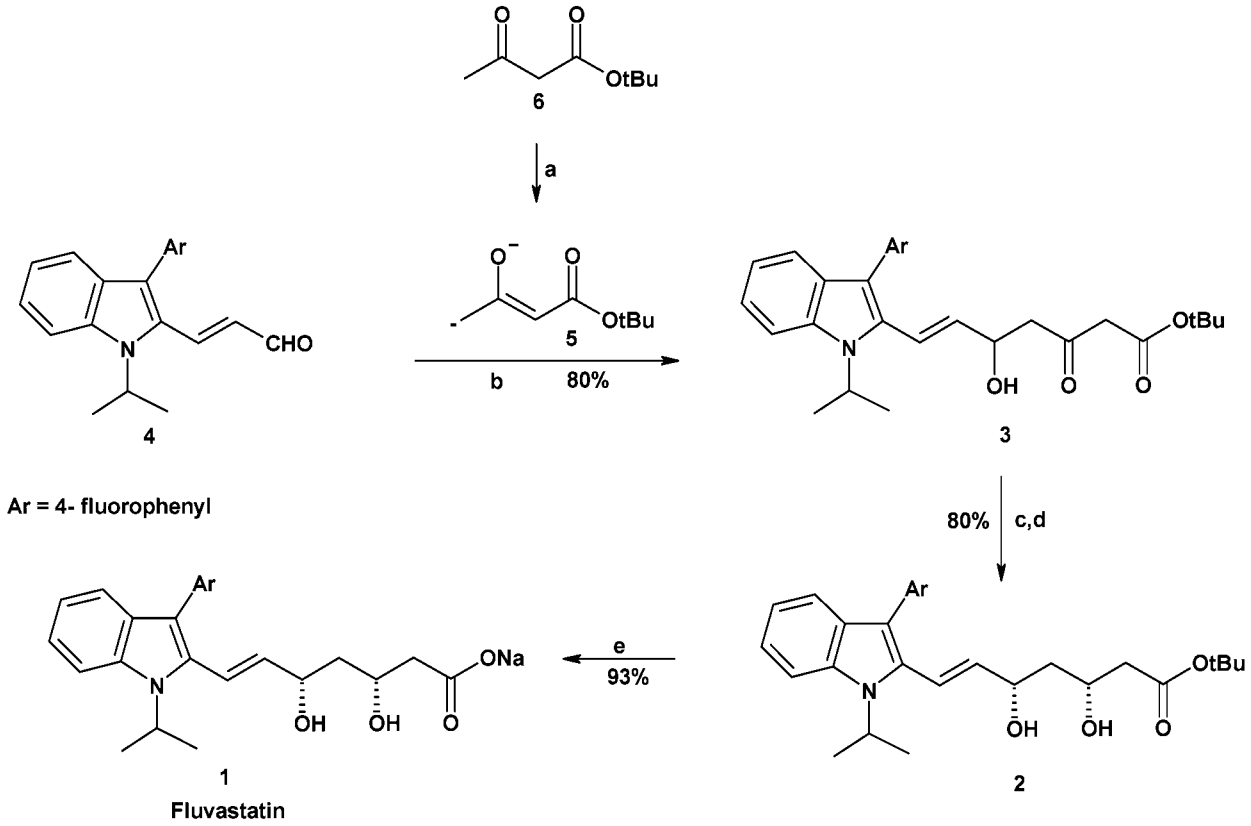
Scheme 1. **Current process for fluvastatin starting from 4**[a]



[a] Reagents and conditions: (a) 1. NaH, 20−25 °C, THF, 2. BuLi, 20−25 °C; (b) THF, 20−25 °C; (c) $NaBH_4$, Et_2BOMe, THF/MeOH, −78 °C; (d) H_2O_2, EtOAc, 20−25 °C; (e) NaOH, H_2O, EtOH, 20−25 °C.

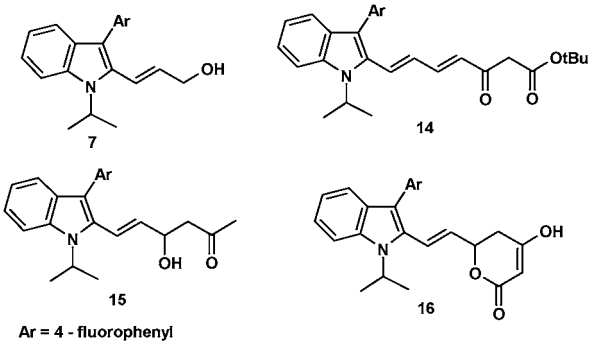


Figure 1. **Potential by-products in the manufacturing of 3.**

pose a quality problem but did have a negative impact on the yield.

Thus, when starting this project, our target was not only to avoid the isolation and drying of **3** but also to increase the yield in the conversion **4** → **3**; if successful, the combination of increased yield and omission of the isolation of **3** would lead to maximal savings. Since compound **3**, particularly in solution, is of limited chemical and thermal stability, this also meant suppression of the potential degradation products **14**, **15**, and **16** during work-up and storage.[11]

(11) The suppression of the formation of three potential by-products, (4*E*,6*E*)-7-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]-3-oxo-hepta-4,6-dienoic acid *tert*-butyl ester, **14**, (*E*)-6-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]-4-hydroxy-hex-5-en-2-one, **15**, and 6-{(*E*)-2-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]-vinyl}-4-hydroxy-5,6-dihydro-pyran-2-one, **16**, can be controlled by observing the correct quench and storage conditions (details see Experimental Section).

In this paper we report how we were able to introduce a new one-pot procedure for the conversion **4** → **2** into production and how the deeper understanding of the underlying chemistry of the aldol condensation helped to identify robust reaction conditions allowing the manufacture of intermediate **3** without isolation in high purity and yield.

3. Results and Discussion

3.1. Avoidance of the Formation of 7. Since in the planned one-pot process for the conversion **4** → **2** no purification by crystallization of the intermediate **3** was envisaged, a nearly quantitative yield for the condensation reaction **4** → **3** was a condition sine qua non for the successful realization of this target. Above all, the mechanism governing the formation of by-product **7** had to be understood and process conditions allowing the suppression of its formation found.

From the analysis of production plant data we were able to hazard a guess that the formation of **7** was somehow connected with the relative stoichiometry of the reaction partners involved. To investigate this hypothesis, an experimental design as summarized in Table 1 was set up. From the results it is evident that the relative stoichiometry of the reaction partners indeed plays a crucial role in the formation of **7** (entries *2*−*5*); reduction of aldehyde **4** to form alcohol **7** always occurs when **4** is in molar excess relative to the dianion **5**. In entry 6, the relative excess of aldehyde **4** was mimicked by adding 0.2 mol equiv of water to the reaction mixture prior to the condensation reaction to artificially

Scheme 2. **Proposed mechanism for the formation of 7**

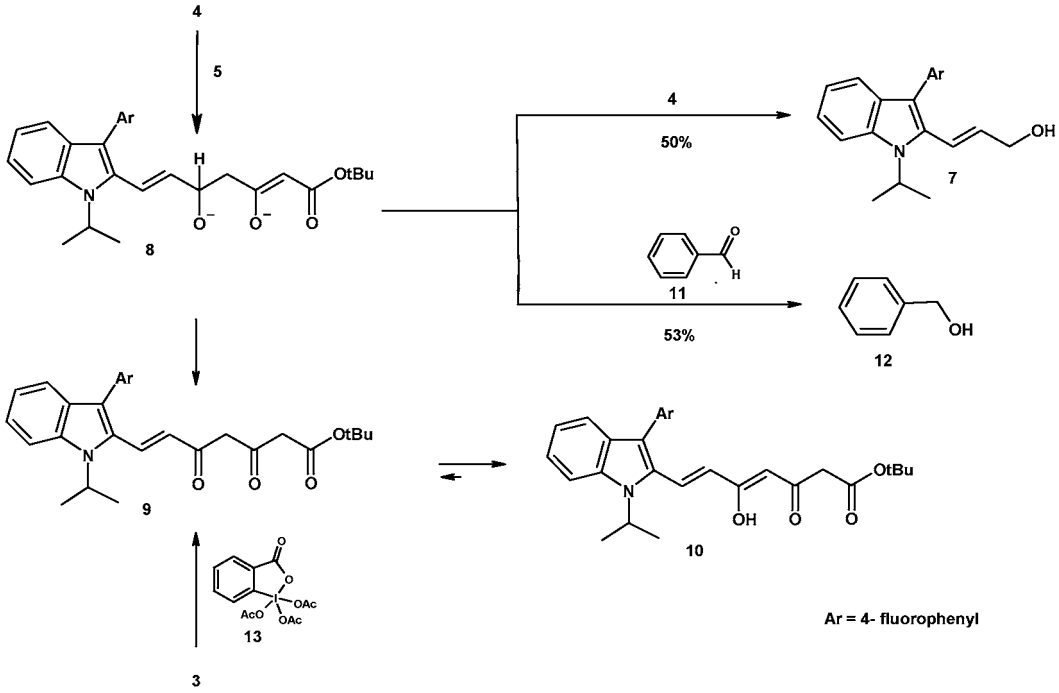


Table 1. **Formation of 7 dependent on the stoichiometry (mol equiv) of the reaction partners**

entry	NaH	**6**	BuLi	**5**	**4**	conversion of **4** (%)	**3** (%)	**7** (%)
1	1.2	1.2	1.2	1.2[a]	1.0	100	98	<0.1
2	1.2	1.2	0.6	0.6[a]	1.0	71	9	38
3	0.6	1.2	1.2	0.6[a]	1.0	82	22	34
4	0.8	0.8	0.8	0.8[a]	1.0	92	31	36
5	1.0	1.0	10	1.0[a]	1.0	99	76	9
6[b]	1.2	1.2	1.2	1.0[a]	1.0	99	59	16

[a] Calculated values. [b] 0.2 mol equiv of water added prior to the addition of **4**.

reduce the molar abundance of **5**. When adding dianion **5** to aldehyde **4** and using the molar ratios of entry 1, the yield of aldol **3** dropped from 98% to 86%, and 7% of alcohol **7** was formed. Thus, not only the "correct" molar ratio of the reaction partners but also the mode of addition is of utmost importance for achieving optimal yield, i.e., aldehyde **4** must be added to dianion **5** and not vice versa.

These results clearly show that reduction to **7** always occurs when the reaction conditions allow the presence of aldehyde **4** together with the initial condensation product, dianion **8** (Scheme 2). To suppress the formation of **7**, sufficient dianion **5** must always be present to instantaneously[12] consume newly added aldehyde **4**. If this is not the case, dianion **8** seems to be capable of acting as a hydride donor, at least towards nonenolizable aldehydes.[13] As shown in Scheme 2, the formation of **7** can be made to be the dominant reaction if aldehyde **4** is added to preformed dianion **8**. Likewise, benzaldehyde **11** is reduced to benzyl alcohol **12** under the same conditions. According to this mechanism, while acting as a reducing agent, dianion **8** must suffer oxidation to form diketoester **9**. Indeed, compound **9** could be isolated from these reaction mixtures, and it was also prepared via oxidation[14] of aldol **3** with Dess−Martin[15] reagent **13**. According to ^{1}H NMR, compound **9** appears to exist predominantly in its enol form **10**.[16] Since under standard reaction conditions (entry 1) virtually no **7** is formed, the proposed hydride transfer reaction from dianion **8** to aldehyde **4** to form **7** must be significantly slower than the desired condensation reaction. Thus, the optimal outcome of the reaction can be fully controlled by careful observation of the correct stoichiometry of the reaction partners and the correct reaction conditions (vide infra).

3.2. Optimized Process for 3. With the knowledge gained as to the suppression of the formation of alcohol **7,** the required high yield for the condensation reaction leading to sufficiently pure **3** was achievable; the way was now free to envisage our main goal, the development of the desired one-pot process for the conversion of **4** to **2**.

In the current process, where dianion **5** is prepared at room temperature, the reaction mixture becomes a thick slurry due to the low solubility of the sodium lithium salt in THF. During the addition of the solution of **4** in THF, the reaction mixture remains initially thick but becomes readily stirrable

(12) To guarantee rapid consumption of **4**, a molar excess of **5** of at least 0.1 mol equiv has to be used. The mol ratios of entry 1 guarantee robust process conditions.

(13) A similar hydride transfer reaction from the lithium enolate of acetaldehyde to nonenolizable aldehydes has been reported by Di Nunno, L.; Scilimati, A. *Tetrahedron* **1988**, *44*, 3639.

(14) To a stirred mixture of **3** (4.66 g, 10 mmol) and dichloromethane (150 mL) was added Dess−Martin reagent (4.70 g, 12.1 mmol) in three portions at −55 °C over a period of 1 h. The clear, yellowish solution was stirred for an additional hour at −30 °C and then washed with saturated sodium carbonate solution containing 5% of sodium thiosulfate. The solvent was removed under vacuum, and from the resulting orange foam a sample of **10** was isolated by silica gel chromatography.

(15) Dess, D. B.; Martin J. C. *J. Org. Chem.* **1983**, *48*, 4156.

(16) Structurally related diketo compounds have been found to exist in their enol forms: Hiyama, T.; Reddy, G. B.; Minami, T.; Hanamoto, T. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 350.

towards the end of the addition. Thus, during the critical initial period, where the reaction mass is viscous and stirring[17] is less efficient, spots of inhomogeneity might be formed in which **4** is in prolonged contact with **8** to form **7**.

Therefore we investigated the means to make the reaction mass less viscous,[18] and we tried to replace the poorly soluble sodium lithium salt **5** by the more soluble dilithium salt of *tert*-butyl acetoacetate. We prepared this salt by (a) replacing sodium hydride with lithium hydride, (b) by using only BuLi, (c) by using BuLi and catalytic amount of LDA, and (d) by using only LDA. In all cases, a clear solution of dilithium *tert*-butyl acetoacetate in THF was obtained, which led after treatment with aldehyde **4** in most cases to good to excellent yield of **3**. In this series, the best results (i.e., virtually quantitative yield) were obtained with the combination BuLi and 10 mol % of diisopropylamine. To achieve optimal yield, the first deprotonation had to be performed at −78 °C and the second at 0 °C. However, the drawbacks of these conditions for a high-volume manufacturing process are apparent: the necessity to implement a low-temperature reactor, the introduction of a new reagent (diispropylamine), and the higher costs due to the use of an additional equivalent of butyl lithium. This convinced us to stay with the current process (i.e., formation of the mono anion with sodium hydride followed by a second deprotonation with BuLi) but to optimize all critical parameters, in particular the reaction temperature of the various process steps.

Eventually, we found that the optimal conditions proved to be 20−25 °C for the monoanion and 0−5 °C for the dianion formation. Surprisingly, when the reaction temperature for the dianion formation is kept at 0−5 °C, the reaction mixture no longer becomes a viscous mass as was the case at 25 °C, but remains a readily stirrable suspension. Under these conditions, only traces of **7** can be detected in the crude reaction mixture, and the yield of **3** is nearly quantitative. When crude **3** was further converted to **2** using the current process conditions, we were able to isolate **2** in the expected yield and required purity. Thus, our first goal, to omit the crystallization and drying of **3** and to reduce the number of solvents used, was met. What remained was to find process conditions allowing an increase in throughput and yield for the low-temperature reduction process **3** → **2**.

3.3. Optimized Process for 2. In the current process, a solution of **3** in methanol/THF is added to a mixture of sodium borohydride and diethylmethoxyborane in THF at −78 °C. The quench is performed with aqueous sodium hydrogen carbonate and ethyl acetate. After distilling off most of the solvents, additional ethyl acetate and aqueous hydrogen peroxide is added at 20−25 °C to cleave boronate species, a process requiring up to 24 h. After several washings, a part of the solvent is evaporated under reduced pressure, heptane is added and the mixture is cooled to room temperature. The precipitated product is isolated by filtration and dried. To remove remaining impurities (in particular the anti-isomer), a second crystallization in an ethyl acetate/heptane mixture is required.

In the re-work of the condensation process **4** → **3** we had been able to eliminate isopropanol and heptane. The elimination of heptane in both crystallization processes for **2** was therefore our first target. However, due to the relatively high solubility of **2** in ethyl acetate, an anti-solvent is required to achieve an optimal yield. Therefore, the elimination of heptane would require replacement of ethyl acetate by a solvent in which **2** has a lower solubility. Among the investigated solvents, isopropyl acetate proved to be the solvent of choice, both due to its lower dissolving power[19] towards **2** and its lower solubility in water,[20] which was considered to be an important argument in view of the rather complex solvent recovery process[21] for the two steps. As a consequence, in the course of our further optimization work we implemented the switch from ethyl acetate to isopropyl acetate, which enabled us to eliminate heptane in both crystallization steps. In addition, further improvements were introduced such as reducing the amount of diethylmethoxyborane and the optimizing of the oxidative treatment[22] of the reaction mixture in the work-up procedure. The reduction reaction itself can be made more selective with respect to the formation of the anti-isomer by decreasing the reaction temperature to below −80 °C. Of course, the limits here are not only given by the reaction rate but also by the cooling capacity of the reaction vessel. Aside from the suppression of the formation of the anti-isomer, the lowering of the reaction temperature also allows the reduction of the excess[23] of sodium borohydride.

4. Summary

The multi-ton manufacturing process for compound **2** had been running for several years in the production plant in two separate process steps, in which intermediate **3** was isolated by crystallization and drying. In the new, re-worked process, intermediate **3** is not crystallized but is used as a crude distillation residue in the next step. On production scale, with the new one-pot process **4** → **2** a throughput increase of 35% and an overall yield increase of 25% was achieved. In addition, the new process allows the elimination of two solvents, leading to a simpler solvent-recovery process.

5. Experimental Section

7-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-5-hydroxy-3-oxo-6-heptenoic acid-1,1-dimethylethyl-

(17) When the current process was introduced into production, significantly larger amounts of **7** were formed than those on laboratory and pilot scale. However, by installing a more efficient stirrer, the situation could be brought quickly under control. In retrospect, with the results of the present investigation, this scale-up phenomenon is now well understood.

(18) Since we wanted to increase not only the yield but also the throughput, we did not consider solving the problem by simply diluting the reaction mixture.

(19) At 25 °C, the solubility of **2** in isopropyl acetate is about 50% lower than that in ethyl acetate.

(20) Solubility in 100 ml of water: ethyl acetate 8.3 g at 20 °C; isopropylacetate 4.3 g at 27 °C.

(21) With the elimination of isopropanol and heptane, a large portion of THF and isopropyl acetate can now be recovered with our solvent recovery process. With the current process conditions, the overall recovery process was much more complex, and with the exception of THF, only a minor portion of the ethyl acetate could be recovered.

(22) By performing the oxidation at 50 °C instead at 25 °C, this treatment could be reduced from ca. 24 h to 3−4 h. The process can be monitored by HPLC and TLC analytics.

(23) The decomposition of sodium borohydride with methanol is catalyzed by diethylmethoxyborane and is relatively fast even at −78 °C (the addition time of **3** should therefore not exceed 4 h). At −85 °C, the excess of sodium borohydride can be reduced by 20%; syn:anti ratio at −85 °C = 99:1.

ester (3), *New* Process Conditions. In a suitable reactor charged with nitrogen, sodium hydride (60% in paraffin oil, 6.0 g, 0.15 mol) was mixed with THF (120 mL) to form a suspension at 20−25 °C. *tert*-Butyl acetoacetate (23.7 g, 0.15 mol) was added within 30 min maintaining the temperature at 20−25 °C and the mixture was further stirred for 15 min. After cooling to 0 °C, butyllithium (1.6 M in hexane, 97.5 mL, 0.15 mol) was added within 60 min, maintaining the temperature at 0 °C. The reaction mixture was stirred at this temperature for a further 30−45 min. A solution of **4** (38.5 g, 0.125 mol) dissolved in THF (100 mL) was added to the reaction mixture, maintaining the temperature at 0 °C. After 60 min stirring at 0 °C, the reaction mixture was quenched with acetic acid (22.6 g, 0.38 mol) and then with water (43.5 mL).[24] The reaction mixture was extracted twice with saturated sodium chloride solution (100 mL) and once with water (50 mL). After removal of the solvents at 30−50 °C and 30 mbar pressure, the evaporation residue containing 57.5 g of **3** (98.8%) was diluted in THF (75 mL) and kept at 0−5 °C (storage solution of **3**).

Formation of Compound 14. If the quench in the above-described experiment is performed only with water, the reaction mixture after the work-up consisted of **3** (10%), **14** (85%), and small amounts of **15** and **16**. Compound **14** was isolated by silica gel chromatography: ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.40 (s, 9 H), 1.63 (d, J = 6.95 Hz, 6 H), 3.59 (s, 2 H), 4.90−5.04 (m, 1 H), 6.09 (d, J = 15.35 Hz, 1 H), 6.41 (dd, J = 15.57, 10.96 Hz, 1 H), 7.05 (t, J = 7.23 Hz, 1 H), 7.20 (t, J = 7.07 Hz, 1 H), 7.29 (t, J = 8.87 Hz, 2 H), 7.32−7.49 (m, 5 H), 7.68 (d, J = 8.46 Hz, 1 H); MS (ES$^+$) m/z 448 (MH$^+$); IR (solid film): 3081, 3047, 2983, 2935, 1626, 1613, 1574, 1542, 1499, 1456, 1412, 1397, 1368, 1345, 1247, 1224, 1158, 1133, 997, 944, 839, 803, 749 (cm^{-1}).

Thermal Stress Experiment with 3 Leading to 14, 15, and 16. The thermal stability of compound **3** was studied by heating a sample of the storage solution of **3** from the aldol condensation (see above) at 50 °C. After 24 h, about 30% of **3** was degraded, and compounds **14**, **15**, and **16** were formed as major by-products. **15** and **16** were isolated by silica gel chromatography. **15:** ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.59 (d, J = 6.95 Hz, 6 H), 2.09 (s, 3 H), 2.41−2.56 (m, 2 H), 4.47−4.59 (m, 1 H), 4.80−4.95 (m, 1 H), 5.16 (d, J = 5.12 Hz, 1 H), 5.73 (dd, J = 16.01, 5.15 Hz, 1 H), 6.66 (dd, J = 16.01, 1.42 Hz, 1 H), 7.01 (t, J = 7.45 Hz, 1 H), 7.13 (t, J = 8.18 Hz, 1 H), 7.23 (t, J = 8.91 Hz, 2 H), 7.40 (dd, J = 8.31, 6.16 Hz, 3 H), 7.63 (d, J = 8.27 Hz, 1 H); MS (ES$^+$) m/z 366 (MH$^+$); IR (solid form): 3467, 3047, 2976, 2937, 2879, 1704, 1605, 1593, 1547, 1503, 1459, 1346, 1219, 1158, 1140, 1116, 1102, 975, 837, 748 (cm^{-1}). **16:** ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.60 (d, J = 6.88 Hz, 6 H), 2.36−2.56 (m, 2 H), 4.79−4.94 (m, 1 H), 4.97 (s, 1 H), 5.00−5.12 (m, 1 H), 5.77 (dd, J = 16.11, 5.94 Hz, 1 H), 6.82 (dd, J = 16.14, 1.04 Hz, 1 H), 7.03 (t, J = 7.48 Hz, 1 H), 7.15 (t, J = 7.14 Hz, 1 H), 7.24 (t, J = 8.81 Hz, 2 H), 7.38−7.46 (m, 3 H), 7.65 (d, J = 8.08 Hz, 1 H), 11.47 (s, 1 H); MS (ES$^+$) m/z 392 (MH$^+$); IR (solid form): 3050, 2970, 2932, 2874, 1889, 1646, 1545, 1501, 1457, 1419, 1371, 1347, 1222, 1156, 1141, 1104, 1094, 1018, 968, 838, 743 (cm^{-1}).

7-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic Acid 1,1-Dimethylethylester (2), *New* Process Conditions. In a suitable reactor charged with nitrogen, sodium borohydride (6.13 g, 0.163 mol) was added to THF (300 mL) at −78 °C. The suspension was stirred at −78 °C during 15 min. A solution of diethylmethoxyborane in THF (50%, 12.5 g, 0.0625 mol) was added within 15 min at −78 °C. A solution of **3** (57.5 g, 0.124 mol) in THF (75 mL) and methanol (100 mL) was added within 2 h at −78 °C. At the end of the addition, the mixture was stirred for 1 h at −78 °C. The reaction mixture was quenched by transferring it to a mixture of isopropylacetate (100 mL), sodium bicarbonate (13.7 g), and water (444 mL). The reactor was rinsed with additional isopropylacetate (100 mL). The mixture was stirred vigorously during at least 60 min until no gas evolution was observed. After phase separation, the organic phase was extracted twice with a solution of sodium chloride (45.9 g) in water (162 mL). The mixture was concentrated at 50 °C and 30 mbar.

The evaporation residue was suspended in isopropylacetate (504 mL) at 50 °C. A solution of hydrogen peroxide 35% (35.7 g, 0.36 mol) was added at 50 °C within 60 min under efficient stirring. The reaction mixture was further stirred during 2−3 h at 50 °C. The reaction mixture was extracted first with a solution of sodium sulfite (16.1 g) in water (207 mL) and then with water (4 × 207 mL) at 55 °C.

The reaction mixture was concentrated at 80 °C (jacket) and 220−50 mbar pressure to a residual volume of 350 mL. The mixture was heated to an internal temperature of 80−85 °C to get a clear solution. After cooling down to 70 °C, the mixture was seeded with a suspension of **2** in isopropylacetate and further stirred at 70 °C during at least 1 h. The suspension was cooled down within 8 h to −10 °C and further stirred at −10 °C during 60 min. The resulting suspension was filtered, and the filter cake washed with cold isopropylacetate (30 mL). The filter cake was suspended in isopropylacetate (200 mL) and heated up to 85 °C to get a clear solution. The mixture was cooled to 70 °C, seeded at 70 °C, and aged at 70 °C for 1 h. The suspension was cooled down within 7 h to 0 °C and further stirred at 0 °C during 60 min. The resulting suspension was filtered and the filter cake washed twice with cold isopropylacetate (30 mL). The filter cake was dried at 50 °C and 125 mbar pressure to give 46.8 g of pure **2** (yield = 80% based on **4**).

3-[3-(4-Fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-2-propen-1-ol (7), via Reduction of 4 with Sodium Borohydride. To a stirred mixture of **4** (30.8 g, 0.10 mol) and methanol (100 mL) was added sodium borohydride (3.8 g, 0.10 mol) in portions at 20 °C over a period of 30 min. The reaction mixture was stirred for 45 min at 20 °C and then quenched by addition to water (200 mL). After addition of *tert*-butylmethylether the phases were separated. The aqueous phases were washed with *tert*-butylmethylether. The combined organic phases were washed with water and dried over sodium sulfate. The solvent was removed under

(24) To avoid the formation of **14**, the pH must reach ca. 5 before water is added.

vacuum, and from the resulting evaporation residue was isolated a sample of **7** by silica gel chromatography. ^{1}H NMR (DMSO-d_6) δ 1.58 (d, 6H), 4.04 (t, 1H), 4.91 (m, 2H), 5.82 (m, 1H), 6.65 (dd, 1H), 7.11 (t, 1H), 7.22 (t, 2H), 7.42 (dd, 3H), 7.62 (d, 1H); MS (ES^+) *m*/*z* 310 (MH^+); IR (solid film): 3252, 3092, 3065, 2984, 2969, 2932, 2870, 1656, 1550, 1536, 1499, 1456, 1371, 1344, 1220, 1155, 1091, 1013, 977, 841, 741 (cm^{-1}).

Reaction of Dianion 8 with 4 To Form 7 and Enol 10. To a stirred mixture of sodium hydride (60% in paraffin oil, 3.0 g, 0.075 mol), and THF (60 mL) was added *tert*-butyl acetoacetate (11.9 g, 0.075 mol) at 20−25 °C over a period of 30 min. The reaction mixture was stirred for additional 15 min at 20 °C. After cooling to 0 °C, butyllithium (1.6 M in hexane, 48.8 mL, 0.075 mol) was added over a period of 60 min at 0 °C. The reaction mixture was stirred for additional 30−45 min. A solution of **4** (38.5 g, 0.125 mol) dissolved in THF (100 mL) was added to the reaction mixture, maintaining the temperature at 0 °C over a period of 2 h. After 60 min of stirring at the same temperature, the reaction mixture was quenched by addition of acetic acid (11.3 g, 0.187 mol) and then with water (22 mL). The reaction mixture was extracted twice with saturated sodium chloride solution (50 mL) and once with water (25 mL). The mixture was concentrated at 30−50 °C and 30 mbar pressure. From the evaporation residue a sample of **10** was isolated by silica gel chromatography. ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.40 (s, 9 H), 1.62 (d, J = 7.02 Hz, 6 H), 3.45 (s, 2 H), 4.90−5.07 (m, 1 H), 5.76 (s, 1 H), 6.11 (d, J = 16.02 Hz, 1 H), 7.07 (t, J = 7.48 Hz, 1 H), 7.24 (t, J = 8.09 Hz, 1 H), 7.30 (t, J = 8.85 Hz, 2 H), 7.37−7.49 (m, 3 H), 7.64−7.78 (m, 2 H), 14.90 (br s, 1 H); MS (ES^+) *m*/*z* 464 (MH^+); IR (solid film): 3436, 3051, 2979, 2935, 1732, 1626, 1585, 1369, 1154, 962, 839, 744 (cm^{-1}).

Reaction of Dianion 8 with Benzaldehyde To Form 10 and Benzyl Alcohol 12. To a stirred mixture of sodium hydride (60% in paraffin oil, 6.0 g, 0.15mol) and THF (120 mL) was added *tert*-butyl acetoacetate (23.7 g, 0.15 mol) at 20−25 °C over a period of 30 min. The reaction mixture was stirred for additional 15 min at 20 °C. After cooling the mixture to 0 °C, butyllithium (1.6 M in hexane, 97.5 mL, 0.15 mol) was added over a period of 60 min at 0 °C. The reaction mixture was stirred for additional 30−45 min. A solution of **4** (38.5 g, 0.125 mol) dissolved in THF (100 mL) was added to the reaction mixture, maintaining the temperature at 0 °C over a period of 1 h. After 30 min stirring at 0 °C a solution of benzaldehyde (13.3 g, 0.125 mol) dissolved in THF (50 mL) was added to the reaction mixture at 0 °C over a period of 60 min. After 60 min stirring at 0 °C, the reaction mixture was quenched by addition of acetic acid (22.6 g, 0.377 mol) and water (22 mL). The reaction mixture was extracted twice with saturated sodium chloride solution (50 mL) and once with water (25 mL). The mixture was concentrated in vacuo to give a reddish oil containing 8 g of **10** and 7 g of benzyl alcohol, according to HPLC analysis.

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