

- [5] B. M. Trost, *Tetrahedron* **1977**, 33, 2615; B. M. Trost, *Acc. Chem. Res.* **1980**, 13, 385. The allyl esters are used as protecting groups for carboxylates and can readily be removed by Pd⁰ in the presence of a nucleophile: P. D. Jeffrey, S. W. McCombie, *J. Org. Chem.* **1982**, 47, 587; S. F. Bochnitschek, H. Waldmann, H. Kunz, *J. Org. Chem.* **1989**, 54, 751. For a recent example, see A. Cotté, B. Bader, J. Kuhlmann, H. Waldmann, *Chem. Eur. J.* **1999**, 5, 922.
- [6] These X-ray crystal structure analyses will be published elsewhere.
- [7] K. Moseley, P. M. Maitlis, *Chem. Commun.* **1971**, 1604.

Stereoselective Mukaiyama–Michael/Michael/Aldol Domino Cyclization as the Key Step in the Synthesis of Pentasubstituted Arenes: An Efficient Access to Highly Active Inhibitors of Cholesteryl Ester Transfer Protein (CETP)**

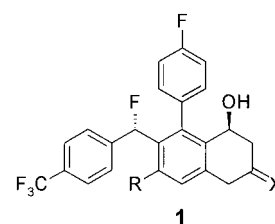
Holger Paulsen,* Stefan Antons, Arndt Brandes, Michael Lögers, Stephan Nicholas Müller, Paul Naab, Carsten Schmeck, Stephan Schneider, and Jürgen Stoltfuß

Dedicated to Dr. Pol Bamelis
on the occasion of his 60th birthday

In spite of a number of successes, the treatment of arteriosclerosis is still a challenge for medicine. In addition to a high LDL-C (low density lipoprotein cholesterol) level, a low HDL-C (high density lipoprotein cholesterol) level is a further, main independent risk factor for coronary heart disease. Whereas the regulation of the LDL-C level by blockade of cholesterol biosynthesis with HMG-CoA reductase (3-hydroxy-methylglutaryl coenzyme A) inhibitors^[1] is established medical practice, the increase in HDL-C levels offers a new and promising therapeutic principle. HDL absorbs cholesterol from the periphery, including the coronary arteries, and carries it to the liver for metabolic degradation. The action of cholesteryl ester transfer protein (CETP) leads to a transfer of cholesteryl ester molecules from HDL to LDL in a triglyceride exchange. The disadvantageous net effect is a reduction in HDL-C level and an increase in LDL-C level.^[2]

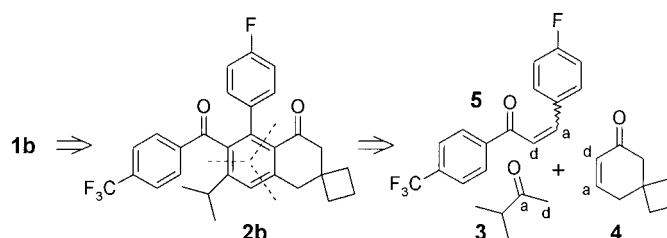
Compounds of structure **1** have been identified as highly active CETP inhibitors (IC₅₀ ≤ 3 nmol L⁻¹).^[3] The complexity of this class of structures and the substance requirements for

further testing demanded an efficient synthesis in order to pave the way for applying this innovative principle. We have tried a number of different strategies and with the example of **1b** we present here a multigram synthesis which features a new domino reaction as the key step.



1
a R = Cyclopentyl X = Spirocyclobutyl
b Isopropyl Spirocyclobutyl
c Isopropyl Dimethyl

Three structural elements are the main contributors to the complexity of **1b**: the spirocyclobutyl system, two stereocenters in sterically demanding positions, and a central, pentasubstituted benzene ring. The first retrosynthetic transformation consisted of interconversion of the stereocenters to a diketone system. Diketone **2b** thus becomes a key intermediate (Scheme 1). Disconnection of the central benzene ring into approximately equally large fragments gives the greatest possible simplification of **2b**. The Mukaiyama–Michael addition is recognized as one of the most reliable



Scheme 1. Retrosynthesis of **1b**.

methods for the synthesis of 1,5-diketones.^[4a] In addition to the obvious 1,5-diketo structure, **2b** contains a strategic carbonyl group concealed behind a “Kekulé double bond” of the central arene. The translation of the resulting synthones into starting materials with alternating acceptor–donor polarization leads to the reagents **3**, **4**, and **5** (Scheme 1).

The enolate formed by the Mukaiyama–Michael addition has already been trapped with aldehydes, acetals, and orthoformates, or by a second, intramolecular Michael acceptor.^[4b,c, 5] An intermolecular Mukaiyama–Michael/Michael/aldol cascade has to our knowledge not been previously published. The underlying domino concept has already been realized,^[6] but the example illustrated here is unique in the degree of substitution and the steric hindrance of the acceptor components, especially **4**.

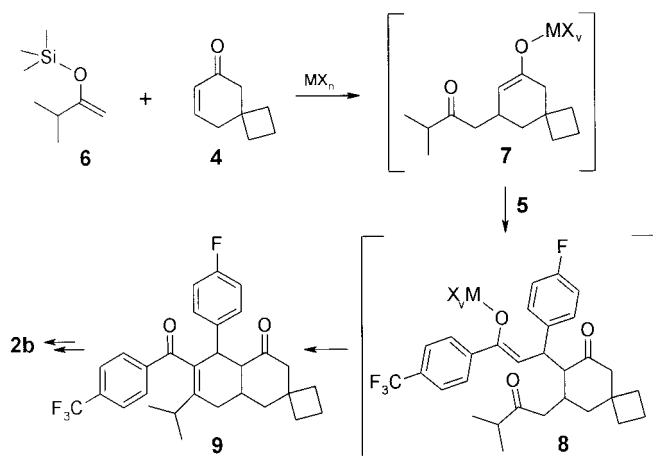
The following concept (Scheme 2) was devised for **2b**: silyl enol ether **6** and **4** yield the enolate **7** under Mukaiyama conditions. Its selective intermolecular 1,4-addition to the chalcone **5** leads to the enolate **8**, which gives **9** in an intramolecular aldol condensation. The cyclization ends a

[*] Dr. H. Paulsen, Dr. A. Brandes, Dr. M. Lögers, Dr. S. N. Müller, Dr. P. Naab, Dr. C. Schmeck, Dr. S. Schneider, Dipl.-Ing. J. Stoltfuß
Bayer AG, Pharmaforschung
PH-R-CF Chemisch-wissenschaftliches Laboratorium
D-42096 Wuppertal (Germany)
Fax: (+49)202-364061
E-mail: holger.paulsen.hp@bayer-ag.de

Dr. S. Antons
Bayer AG, PH-OP-CE Verfahrensentwicklung

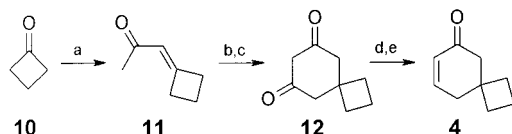
[**] We thank Dr. J. Benet-Buchholz for the X-ray structure analysis and colleagues of PH-R-Strukturchemie for providing the analytical data.

Supporting information for this article is available on the WWW under <http://www.wiley-vch.de/home/angewandte/> or from the author.



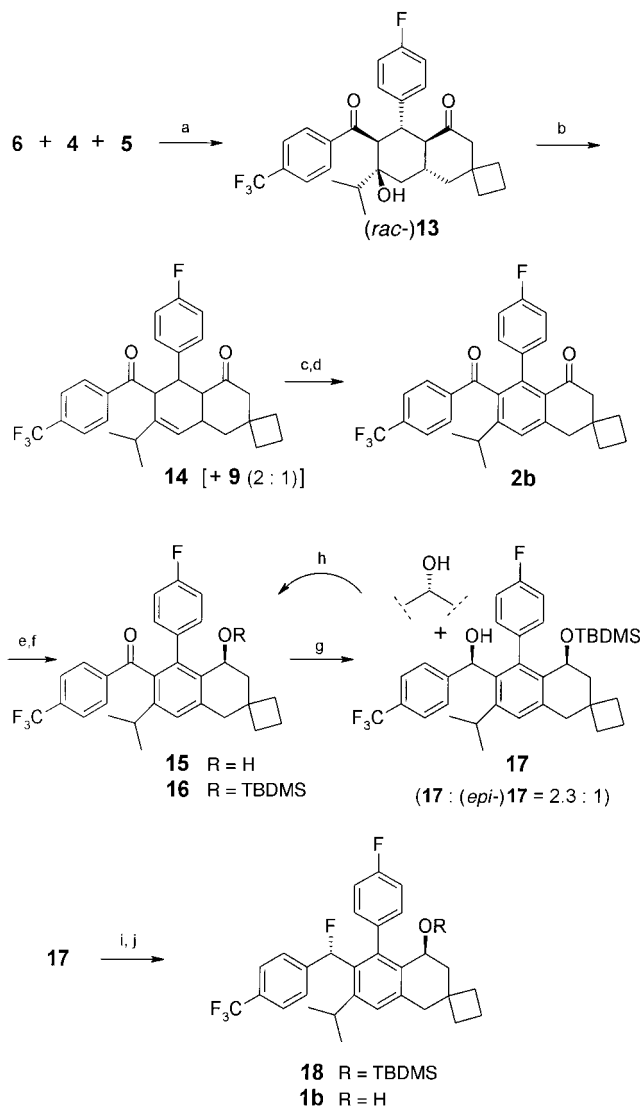
Scheme 2. Concept for the synthesis of the key compound **2b**.

reaction sequence in which the complete carbon framework of **2b** is constructed. The silyl enol ether **6** was formed from ketone **3** in the usual manner.^[7] The (*E*)-chalcone **5** was obtained in 95 % yield by the acid-catalyzed aldol condensation of 4-(trifluoromethyl)acetophenone and 4-fluorobenzaldehyde. Following preliminary investigations with cyclohexenone the sterically demanding spiro compound **4** was synthesized (Scheme 3). To this effect, the cyclobutanone **10** was first transformed into the enone **11** in a Wittig reaction.



Scheme 3. Synthesis of **4**. a) $\text{Ph}_3\text{P}=\text{CHCOCH}_3$, silicon oil, 100 °C, cat. PhCO_2H , 87 %; b) $\text{CH}_2(\text{CO}_2\text{Me})_2$, NaOMe, MeOH, 65 °C; c) aq. KOH, reflux, 20 % hydrochloric acid, pH 3–5, 99 %; d) isobutanol, toluene, cat. *p*-TsOH, azeotropic distillation; e) RedAl (65 % in toluene), 40–50 °C, 77 % relative to **12**. Ts = 4-methylphenylsulfonyl, RedAl = sodium bis-(2-methoxyethoxy)aluminum hydride.

The addition of dimethyl malonate and cyclization by Claisen condensation followed by hydrolysis and decarboxylation gave the dimedone analogue **12**. Enol ether synthesis and an ensuing reduction with RedAl gave the desired starting material **4**. In the key reaction, **6** and **4** in dichloromethane at about –5 °C were transformed into *rac*-**13** by successive addition of four equivalents of $\text{TiCl}_3(\text{O}i\text{Pr})$ in dichloromethane and **5** (Scheme 4).^[8] After aqueous workup, the product is readily isolated diastereomerically pure in 42 % yield by simple crystallization from petroleum ether. The all-equatorial arrangement of the substituents and the axial position of the hydroxyl functionality were confirmed by X-ray structure analysis.^[9] Until now the formation of only one additional diastereoisomer was detected to an extent of 10 % or less.^[10] The aldol condensation to **9** illustrated in Scheme 2 was not observed in spite of the antiperiplanar arrangement of the hydroxyl group and the H atom α to the carbonyl group.^[9] The correct establishment of the required connectivities was all that was needed to be achieved. Therefore, the excess of molecular complexity which was produced with the stereo-



Scheme 4. Synthesis of **1b**: a) $\text{TiCl}_4/\text{Ti}(\text{O}i\text{Pr})_4$ (3/1; i.e., 4 equiv of $\text{TiCl}_3(\text{O}i\text{Pr})$), dichloromethane, –5 °C, 42 %; b) pyridine, SOCl_2 , 0 °C, 83 %; c) NCS, cat. $(\text{PhCO}_2)_2$, dichloromethane, RT, 85 %; d) DBU, dioxane, 5, 96 °C, 64 %; e) (1*R*,2*S*)-1-aminoinidan-2-ol (0.3 equiv), $\text{BH}_3\text{--NEt}_2\text{Ph}$ (3 equiv), THF, RT, 78 %; 94 % *ee* for the crude product; f) TBDMSCl, NEt_3 , DMAP, DMF, 70 °C, 80 %; g) LAH, THF, 0 °C → RT, 55 % **17**, >99 % *ds*; h) MnO_2 , dichloromethane, RT, 77 % **16**; i) DAST (Et_2NSF_3), toluene, –70 °C → –60 °C, 75 %; j) TBAF, THF, RT, 87 %, >99 % *ee*, >99 % *ds*. NCS = *N*-chlorosuccinimide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TBDMS = *tert*-butyldimethylsilyl, DMAP = 4-(dimethylamino)pyridine, LAH = lithium aluminum hydride, TBAF = tetra-*n*-butylammonium fluoride.

selectively generated stereopentad was dismantled by subsequent aromatization with removal of all stereocenters. The sterically highly loaded cyclohexanol derivative **13** was thus subjected to a double halogenation–elimination sequence with subsequent oxidation at the cyclohexadiene stage (see Scheme 4).

The system resisted shorter aromatization strategies, for example the catalytic dehydrogenation at the cyclohexene stage, because of the all-*trans* arrangement of the hydrogen atoms and the large increase in steric interactions. Only reaction in a sulfur melt also afforded the arene **2b** successfully.

A mixture of the elimination products **14** and **9** was obtained rapidly and in high yield by treatment of *rac*-**13** with thionyl chloride in pyridine. Allylic halogenation gave a regioisomeric mixture which provided **2b** after elimination in the presence of an oxidizing agent. To introduce the stereocenters **2b** was next regio- and enantioselectively reduced to the oxoalcohol **15**. A variant of the Corey–Bakshi–Shibata (CBS) reduction makes use of *cis*-1-aminoindane-2-ol as the source of chirality.^[11] With this procedure, the tetralone system in the highly sterically hindered **2b** was reduced with high enantioselectivity (94% *ee* in the crude product) and yield (78% of **15** after crystallization) with complete differentiation of the two oxo groups. After protection of the hydroxyl functionality as the TBDMS ether (**16**) the internal 1,5-induction of the stereocenter mediated by the biphenyl system permitted a diastereoselective reduction of the second oxo function with LAH in favor of the desired isomer **17** (**17:epi-17** = 2.3:1). This was isolated from the mixture by crystallization. The alcohols remaining in the mother liquor, **17** and *epi*-**17**, could be reconverted into **16** by oxidation of the double benzylic position with manganese dioxide. By reaction of the unprotected hydroxyl functionality with DAST (Et₂NSF₃) **17** is converted with inversion into the fluoro compound **18**. The final deprotection with TBAF yields the target compound **1b** in diastereomeric and enantiomeric pure form (> 99% *ds*, > 99% *ee* after crystallization).

The present synthesis of **1b**, in its longest linear sequence 14 steps, can be carried out without any chromatographic purification and can be converted in a kilogram-scale process. The way is thus open for the in-depth evaluation of CETP inhibition as a therapeutic principle.

Experimental Section

rac-**13**: To a solution of **6** (72 mmol) and **4** (60 mmol) in dichloromethane (40 mL) are added simultaneously TiCl₄ (183 mmol) and Ti(O*i*Pr)₄ within 30 min under argon at –7 to –1 °C. After 5 min solid **5** (60 mmol) is added, during which time the temperature increases to 3 °C. The reaction mixture is stirred for 5 min with cooling, then for 2 h at room temperature. After workup with 1N hydrochloric acid, washing with water, drying over sodium sulfate, and removal of the solvent the residue is crystallized from petroleum ether. The product *rac*-**13** is obtained in 42% yield.

Received: June 16, 1999 [Z13574IE]

German version: *Angew. Chem.* **1999**, *111*, 3574–3576

Keywords: asymmetric synthesis • cyclizations • domino reactions • drug research • Mukaiyama–Michael additions

- [4] a) K. Narasaka, K. Soai, Y. Aikawa, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 779–783; b) T. Mukaiyama, S. Kobayashi, *Heterocycles* **1987**, *25*, 205–211; c) N. Giuseppone, Y. Courtaux, J. Collin, *Tetrahedron Lett.* **1998**, *39*, 7845–7848.
- [5] a) H. Hagiwara, A. Okano, H. Uda, *J. Chem. Soc. Chem. Commun.* **1985**, 1047; b) P. G. Klimko, D. A. Singleton, *J. Org. Chem.* **1992**, *57*, 1733–1740; c) H. Hagiwara, Y. Yamada, H. Sakai, T. Suzuki, M. Ando, *Tetrahedron* **1998**, *54*, 10999–11010.
- [6] a) C. Wakselman, M. Mondon, *Tetrahedron Lett.* **1973**, 4285–4288; b) G. H. Posner, S.-B. Lu, E. Asirvatham, *Tetrahedron Lett.* **1986**, *27*, 659–662; c) G. H. Posner, E. Asirvatham, *Tetrahedron Lett.* **1986**, *27*, 663–666; d) G. H. Posner, S.-B. Lu, E. Asirvatham, E. F. Silversmith, E. M. Shulman, *J. Am. Chem. Soc.* **1986**, *108*, 511–512; e) S. Marczak, K. Michalak, Z. Urbańczyk-Lipkowska, J. Wicha, *J. Org. Chem.* **1998**, *63*, 2218–2223; reviews: f) G. H. Posner, *Chem. Rev.* **1986**, *86*, 831–844; g) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 137–170; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131–163; h) M. Ihara, K. Fukumoto, *Angew. Chem.* **1993**, *105*, 1059–1071; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1010–1022; i) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136.
- [7] a) H. O. House, L. J. Czuba, M. Gall, H. D. Olmstead, *J. Org. Chem.* **1969**, *34*, 2324–2336; b) T. Bach, K. Jödicke, *Chem. Ber.* **1993**, *126*, 2457–2466.
- [8] Because of the oxygen-containing functional groups 2–4 equivalents of titanium reagent are necessary. According to reference [4a], cyclohexenone and **6** are labile towards titanium tetrachloride. TiCl₄(O*i*Pr)₄ on the other hand proved to be too weak an inducing agent for the desired reaction. TiCl₃(O*i*Pr)₃ can be freshly prepared by the (exothermic) mixing of TiCl₄ and Ti(O*i*Pr)₄ in a ratio of 3:1 or by parallel addition of both components. A modification of this reaction has meanwhile been carried out on a kilogram scale.
- [9] The C–OH und C=O bonds are almost parallel. In addition, the IR and ¹H NMR spectra suggest a hydrogen bond between the two groups (low-field shift and W-coupling of the OH hydrogen atom with an H atom of the neighboring AB system). By complexation with titanium this conformation should be maintained in the reaction mixture. Thus, the π orbitals of the carbonyl group and the σ C–H bond in the α position are almost orthogonal to each other. Therefore, acidification of the α H atom lacks conjugative stabilization. In addition, elimination leads to greater steric hindrance of the neighboring substituents.
- [10] The ¹H NMR spectrum of this diastereomer indicates the absence of the intramolecular hydrogen bridge.
- [11] a) B. Di Simone, D. Savoia, E. Tagliavini, A. Umani-Ronchi, *Tetrahedron: Asymmetry* **1995**, *6*, 301–306; b) review: A. K. Ghosh, S. Fidanzé, C. H. Senanayake, *Synthesis* **1998**, 937–961.

- [1] “Statins” such as cerivastatin; reviews: a) R. S. Rosenson, *Arch. Intern. Med.* **1996**, *156*, 1278–1284; b) M. J. Tikkanen, *Curr. Opin. Lipidol.* **1995**, *6*, 360–364.
- [2] a) M. Sugano, N. Makino, S. Sawada, S. Otsuka, M. Watanabe, H. Okamoto, M. Kamada, A. Mizushima, *J. Biol. Chem.* **1998**, *273*, 5033–5036; b) A. S. Plump, L. Masucci-Magoulas, C. Bruce, C. L. Bisgaier, J. L. Breslow, A. R. Tall, *Arterioscler. Thromb. Vasc. Biol.* **1999**, *19*, 1105–1110; c) review: C. G. Stevenson, *Crit. Rev. Clin. Lab. Sci.* **1998**, *35*, 517–546.
- [3] Significant HDL-C increase in hamsters and hCETP mice at doses of <1 mg kg^{–1} p.o. (p.o. = per os, oral administration).