(3475 unique reflections, $R_{\text{int}} = 0.1492$, $\theta < 25.0°$) were collected on a Bruker SMART CCD diffractometer. The structure was solved and refined as for **2**:[2a] $wR2 = 0.1147$, conventional $R = 0.0494$ for F values of 1407 reflections with $F_o^2 > 2\sigma(F_o^2)$, and $S = 0.802$ for 259 parameters. Isotropic H atoms bonded to C were constrained. Max./min. residual electron density: $0.15/-0.16\ \text{e}\,\text{Å}^{-3}$.[2b]

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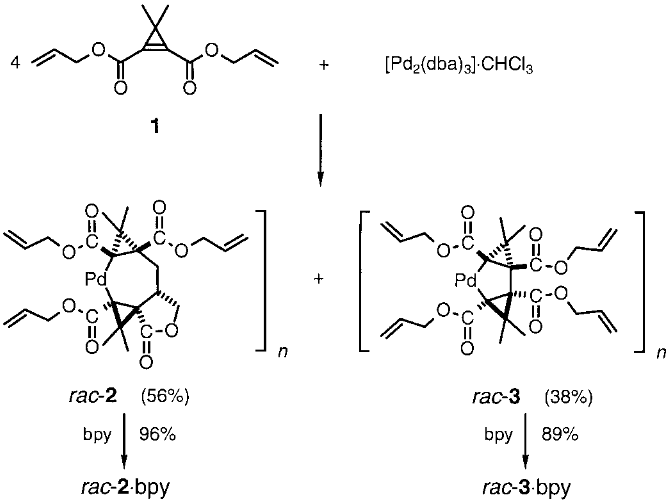
First and Highly Diastereoselective Synthesis of Palladepanes[**]

A. Stephen K. Hashmi,* Andreas Rivas Nass,
Jan W. Bats, and Michael Bolte

Although many palladium-catalyzed reactions are supposed to proceed via palladacyclo[*n*]alkanes,[1] such species have, with one singular exception, never been isolated or detected for compounds with more than five ring atoms! The high tendency of such intermediates to form the corresponding cyclo[$n-1$]alkanes by a fast reductive elemination is probably responsible for this observation. The exception mentioned above is a diphosphane complex of a nine-membered palladacycloalkane derivative that was formed in the reaction of 3,3-dimethylcyclopropene with a Pd^0 precursor.[2] Here we report the first synthetic approach to palladacycloheptane derivatives.

Since several of our efforts to achieve an intermolecular "mixed" oxidative cyclization between a cyclopropene and another unsaturated organic molecule at a Pd^0 center failed, we prepared **1**, which offered a terminal double bond as an intramolecular reaction partner at an appropriate distance. In the reaction of **1** with $[\text{Pd}_2(\text{dba})_3]\cdot\text{CHCl}_3$, two products were formed. The minor product could be identified as the palladatricyclo[4.1.0.0^{2,4}]heptane (PTH) derivative *rac*-**3** (Scheme 1). We had observed this mode of reaction many times before for cyclopropene-1,2-dicarboxylates.[3] The major product turned out to be the seven-membered palladacycloalkane derivative *rac*-**2**. As reported before for the PTHs, the palladacycloalkanes *rac*-**2** and *rac*-**3**, which would be coordinatively unsaturated, are stabilized by the formation of coordination polymers. The PTHs that possess no olefinic side chains are readily dissolved in coordinating solvents like acetone or acetonitrile, and complexes with two molecules of these easily exchangable solvents were obtained.[3b,c] In contrast, the ^{1}H NMR spectra of *rac*-**2** and *rac*-**3** in these solvents showed that they are still aggregated (probably through intermolecular coordination of the olefin moieties). As PTHs are known to form stable complexes with bidentate ligands,[3a,d,e] the 2,2′-bipyridyl (bpy) ligand was used to prepare the monomeric complexes *rac*-**2**·bpy (Table 1) and *rac*-**3**·bpy from *rac*-**2** and *rac*-**3**.



Scheme 1. Cyclization of cyclopropene **1**. bpy = 2,2′-bipyridyl, dba = dibenzylideneacetone.

An X-ray crystal structure analysis was carried out for *rac*-**2**·bpy (Figure 1).[4] Thus the connectivity as well as the stereochemical assignment was proven unambiguously. We could not detect the other diastereomer of *rac*-**2** possessing a *cis* arrangement of the two three-membered rings annelated to the central seven-membered ring. The high yields of *rac*-**2** and *rac*-**3** (sum 94%) clearly showed that other processes which one could have feared to occur with the allyl ester moieties of the molecules (formation of π-allyl–Pd^{II} species with the stoichiometric amount of Pd^0, like in the Tsuji–Trost reaction)[5] were of no significance under these conditions.

We then tested whether the double bond of the allyl ester is capable of directing the regioselectivity of the cyclization. The cyclopropene **4** bearing methyl and allyl ester moieties led to the maximum number of constitutional isomers one could expect. As PTHs the three isomers *rac*-**7**, *rac*-**8**, and *rac*-**9** were formed (Scheme 2). While *rac*-**8** could easily be assigned by its

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Table 1. Selected spectroscopic data for *rac*-**2** · bpy and *rac*-**13**.

rac-**2** · bpy: IR (NaCl, film): $\tilde{\nu} = 3142, 3082, 2935, 1754, 1714, 1682\ \text{cm}^{-1}$; ^{1}H NMR (400 MHz, [D$_6$]acetone): $\delta = 1.54$ (s, 3H), 1.61 (s, 3H), 1.69 (s, 3H), 1.74 (s, 3H), 2.39–2.51 (m, 3H), 4.13–4.23 (m, 4H), 4.33–4.38 (m, 1H), 4.40–4.41 (m, 1H), 4.43–4.48 (m, 1H), 4.48–4.61 (m, 1H), 4,79–4.83 (m, 1H), 4.84–4.88 (m, 1H), 5.13–5.22 (m, 3H), 5.29–5.35 (m, 1H), 5.68–5.78 (m, 2H), 5.91–6.01 (m, 1H), 7.73–7.77 (m, 2H), 8.16–8.21 (m, 2H), 8.31–8.34 (m, 2H), 9.17–9.22 (m, 2H); ^{13}C NMR (62.9 MHz, [D$_6$]acetone): $\delta = 20.7$ (q), 21.2 (q), 26.8 (q), 27.7 (q), 33.9 (s, 2C), 34.3 (s), 34.7 (s), 35.1 (t), 37.4 (d), 45.3 (s), 48.6 (s), 64.2 (t), 64.6 (t), 65.6 (t), 74.7 (t), 116.1 (t), 116.3 (t), 118.0 (t), 122.9 (d), 123.0 (d), 126.3 (d), 126.4 (d), 134.1 (d), 134.7 (d), 134.8 (d), 139.9 (d, 2C), 153.6 (d), 153.8 (d), 155.9 (s), 156.0 (s), 173.1 (s), 174.0 (s), 174.2 (s), 177.0 (s); FAB-MS (positive ion, *m*-nitrobenzyl alcohol): m/z (%): 734 (1, [M^+]), 677 (3, [$M^+ - C_3H_5O$]), 512 (2), 157 (100); elemental analysis calcd for $C_{36}H_{40}N_2O_8Pd$ (735.1): C 58.82, H 5.48, N 3.81; found: C 58.54, H 5.53, N 3.95

rac-**13**: IR (NaCl, film): $\tilde{\nu} = 2920, 1752, 1724, 1676, 1396, 1281, 1232, 1153\ \text{cm}^{-1}$; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 2.41$ (d, $J = 14.7$ Hz, 2H), 2.93–2.99 (m, 2H), 3.50–3.55 (m, 2H), 4.04 (dd, $J = 9.6$ Hz, 3.9 Hz, 2H), 4.53 (t, $J = 4.7$ Hz, 2H), 4.72–4.75 (m, 4H), 5.26–5.37 (m, 4H), 5.91–6.01 (m, 2H); ^{13}C NMR (101 MHz, CDCl$_3$): $\delta = 38.7$ (t), 40.1 (d), 66.7 (t), 72.3 (t), 119.5 (t), 131.3 (d), 131.4 (s), 143.0 (s), 167.3 (s), 168.3 (s); elemental analysis calcd for $C_{20}H_{20}O_8$ (388.4): C 61.85, H 5.19; found: C 61.61, H 5.20

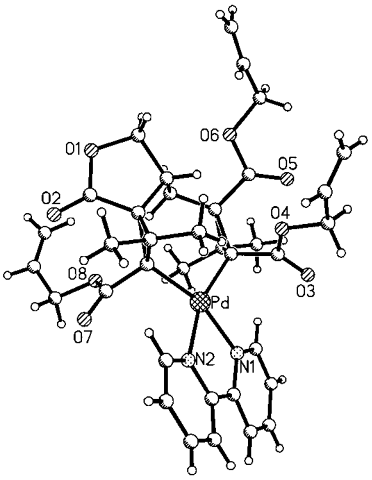
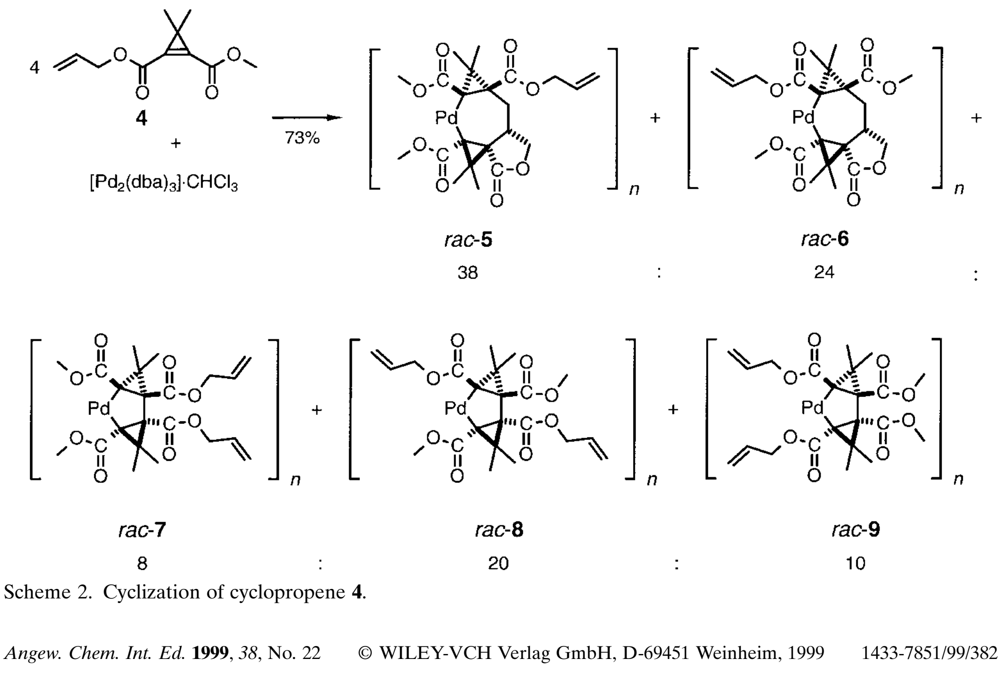


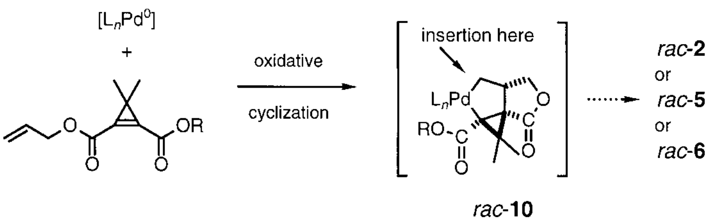
Figure 1. X-ray crystal structure of *rac*-**2** · bpy (ORTEP plot).



Scheme 2. Cyclization of cyclopropene **4**.

C_1 symmetry, *rac*-**7** and *rac*-**9** were C_2-symmetrical. We again prepared the bpy complexes *rac*-**7** · bpy, *rac*-**8** · bpy, and *rac*-**9** · bpy, and from the latter obtained crystals suitable for a crystal structure analysis.[6] Therefore, the assignments for *rac*-**7** and *rac*-**9** were possible. The relative yields of *rac*-**7**, *rac*-**8**, and *rac*-**9** (see Scheme 2) basically reflected the statistical ratio one could expect, so no directing effect of the vinyl group in the side chain was observed with the PTHs. As palladacycloheptane derivatives, *rac*-**5** and *rac*-**6** could be isolated. For a clean structural assignment the complexes *rac*-**5** · bpy and *rac*-**6** · bpy were prepared and investigated by crystal structure analysis.[6] Interestingly the major product was the one with the allyl group far away from Pd; again, both complexes showed the *trans* arrangement of the two cyclopropyl rings annelated to the palladacyle. The relative yields of the isolated products *rac*-**5**–*rac*-**9** corresponded well to the relative ratios determined in the crude product by HPLC.

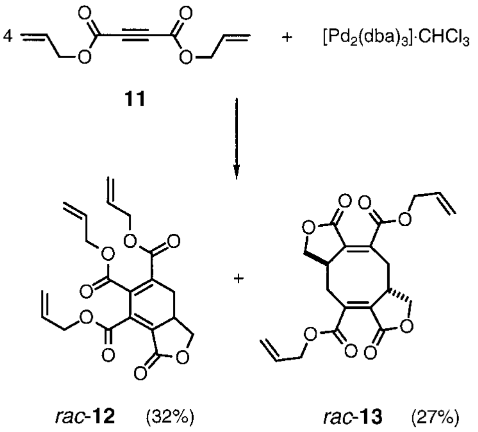
How were the products *rac*-**2**, *rac*-**5**, and *rac*-**6** formed? It was reasonable to assume that first the strained cyclopropene coordinates to palladium, and then the vinyl group reacts as an intramolecular partner in an oxidative cyclization. Then the intermediate *rac*-**10** would be formed (Scheme 3) containing two different Pd–C bonds. A second (reactive) cyclopropene molecule then inserts only into the Pd–CH$_2$ bond and not into the Pd–cyclopropyl bond (in this step the diastereoselection also takes place). This would be in accordance with the behavior of the PTHs, where we observed that additional cyclopropene (as well as other olefins)[3e] did not insert into the Pd–cyclopropyl bonds of the five-membered palladacyloalkanes.[3c] The end products *rac*-**2**, *rac*-**5** or *rac*-**6** then contain two Pd–cyclopropyl bonds that seemed to be quite stable (kinetically and/or thermodynamically). In neither the seven-membered palladacycloalkanes *rac*-**2** and *rac*-**6** nor the five-membered palladacycloalkanes *rac*-**8** and *rac*-**9** did we observe another insertion of the vinyl group offered intramolecularly. These compounds were perfectly stable



Scheme 3. Intermediate in the cyclization of cyclopropenes with allyl ester substituents. L = dba or solvent; R = CH$_2$CH=CH$_2$, CH$_3$.

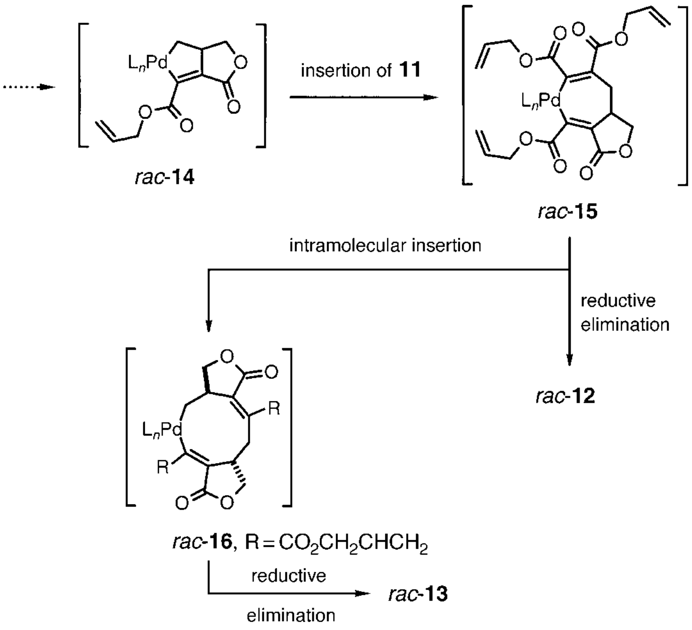
up to 50 °C! Therefore, it might not be a coincidence that the only other known palladacycloalkane with more than five ring atoms also has two Pd–cyclopropyl bonds.

To test this concept we treated the anlogous diallyl acetylenedicarboxylate **11** (we concidered PTHs to be "bishomo" palladoles) with Pd^0 under the same conditions (which are also the standard conditions for the formation of the analogous palladoles).[7] In this case no palladacycles could be isolated; only the two products *rac*-**12** and *rac*-**13**[6] (Table 1) were obtained (Scheme 4).



Scheme 4. Cyclization of acetylenedicarboxylate **11**.

The formation of these products can be explained by an intermediate *rac*-**15**, which corresponds to *rac*-**2**, *rac*-**5**, and *rac*-**6**. An initial oxidative cyclization would form *rac*-**14**, and then insertion of a second alkyne into the Pd–CH$_2$ bond would give the seven-membered ring *rac*-**15**. Subsequent reductive elimination would lead to *rac*-**12**, whereas intramolecular (regio- as well as diastereoselective!) insertion of the alkene into the nine-membered ring would provide *rac*-**16**, which then reductively eliminates *rac*-**13** (Scheme 5). Both steps—the reductive elimination of *rac*-**15** to *rac*-**12** and the insertion that transforms *rac*-**15** into *rac*-**16** (or, in other words, the fact that no palladacylces were isolated)—demonstrated that the Pd–C bonds in *rac*-**14**, *rac*-**15**, and *rac*-**16** are more reactive than in the stable palladacyles *rac*-**2**, *rac*-**5**, and *rac*-**6**.



Scheme 5. Intermediates in the cyclization of **11**. L = dba or solvent.

The synthesis of palladacycloheptanes reported here will now allow the investigation of the reactivity of this new class of organometallic compounds. The stability of such metallacycles formed from cyclopropenes might also allow the isolation of analogous intermediates involved in transition metal catalyzed reactions of alkenes or alkynes.

Experimental Section

rac-**2**·bpy: A solution of **1** (330 mg, 1.40 mmol) in acetone (4 mL) was added to a well-stirred solution of [Pd$_2$(dba)$_3$]·CHCl$_3$ (300 mg, 290 µmol) in acetone (70 mL) at room temperature. After 1 h the solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (eluent: hexanes/acetone 2/1) to give *rac*-**2** (187 mg, 56 %) and *rac*-**3** (127 mg, 38 %). Derivative *rac*-**2** (187 mg, 322 µmol) was dissolved in MeCN (20 mL) and CH$_2$Cl$_2$ (4 mL). 2,2′-Bipyridyl (54.2 mg, 347 µmol) was added in one portion, and after 10 min the solvent was removed in vacuo. Column chromatography on silica gel (eluent: hexanes/acetone 4/1) provided *rac*-**2**·bpy (227 mg, 96 %). Crystals for the structure analysis were grown from hexane/ethyl acetate at 4 °C.

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[4] Crystal structure analysis of *rac*-**2**·bpy: Siemens CCD three-circle diffractometer, Mo$_{K\alpha}$ radiation ($\lambda = 0.71073$ Å), ω scans, empirical absorption correction with SADABS (G. M. Sheldrick, a Program for Absorption Correction of Area Detector Data, Universität Göttingen, Germany, **1996**), the structure was solved by direct methods and refined with SHELXL-97 (G. M. Sheldrick, a Program for the Refinement of Crystal Structures, Universität Göttingen, Germany, **1997**) by full-matrix least-square methods against F^2. Hydrogen atoms were placed on ideal positions and refined with fixed isotropic displacement parameters using a riding model. $C_{40}H_{48}N_2O_{10}Pd \cdot CH_3CO_2CH_2CH_3$: $0.9 \times 0.45 \times 0.45$ mm, triclinic, space group $P\bar{1}$; $a = 12.5620(8)$, $b = 13.1135(11)$, $c = 13.4805(13)$ Å, $\alpha = 117.697(8)$, $\beta = 94.107(7)$, $\gamma = 97.666(8)°$; $V = 1925.9(3)$ Å^3, $Z = 2$; $\rho_{calcd} = 1.420$ g cm^{-3}; $\mu = 0.541$ mm^{-1}, min./max. transmission 0.862/1.000; $2\theta_{max} = 62.9°$; 143(2) K; of 34664 measured reflections, 10828 were independent; 476 parameters refined; $R1 = 0.055$, $wR2 = 0.182$; min./max. residual electron density 1.533/ – 1.221 e Å^{-3}. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-127844. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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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)[**]

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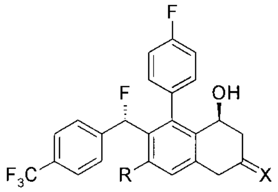
Dedicated to Dr. Pol Bamelis
on the occasion of his 60th birthday

In spite of a number of successes, the treatment of arteriosclerosis is still a challenge for medicine. In addition to a high LDL-C (*l*ow *d*ensity *l*ipoprotein *c*holesterol) level, a low HDL-C (*h*igh *d*ensity *l*ipoprotein *c*holesterol) 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-*h*ydroxy-*m*ethyl*g*lutaryl 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]

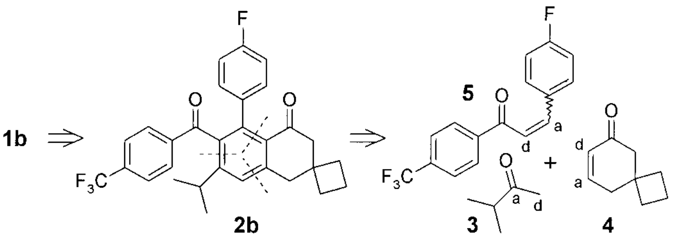
Compounds of structure **1** have been identified as highly active CETP inhibitors ($IC_{50} \leq 3\ nmol\,L^{-1}$).[3] The complexity of this class of structures and the substance requirements for further testing demanded an efficient synthesis in order to pave the way for applying this innovative principle. 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 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).



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

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

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

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