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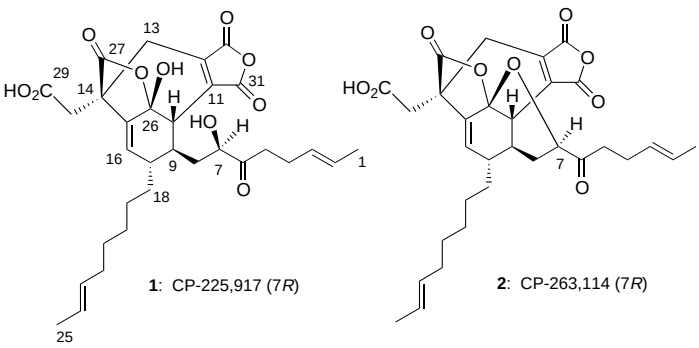
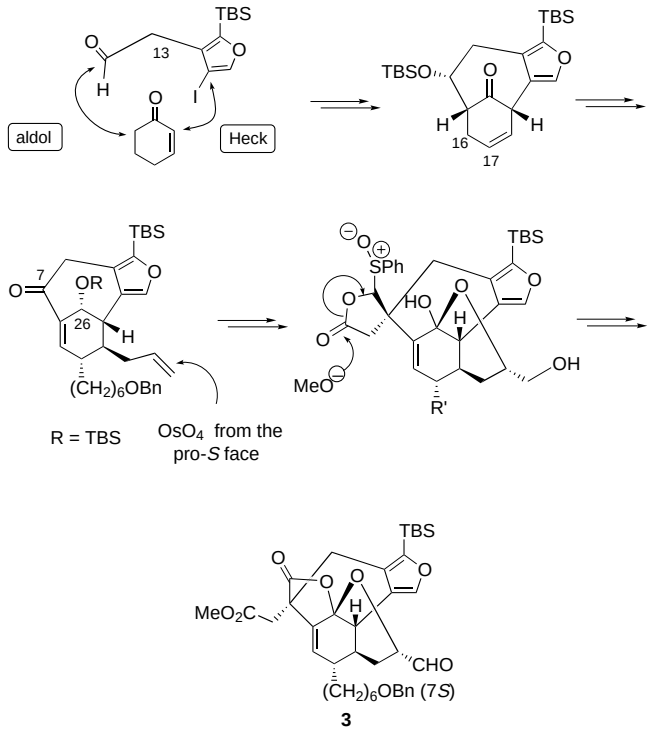
Discovery Through Total Synthesis—Epimerization at C7 in the CP Compounds: Is (7*S*)-CP-263,114 a Fermentation Product?**

Dongfang Meng, Qiang Tan, and Samuel J. Danishefsky*

The goal of accomplishing the total syntheses of CP-225,917 (**1**) and CP-263,114 (**2**) has attracted the active participation of a variety of research groups.[1–3] These substances inhibit farnesyltransferase and squalene synthase activity. While the biological potential, if any, of agents that combine both activities is far from demonstrated, chemists have been attracted to this challenge by the novel molecular architecture of these target compounds. Elsewhere, we have described an approach to the synthesis of the CP series that delivered compound **3**, with the full framework to reach the target structure (Scheme 1).[3c]





Scheme 1. Synthesis of **3**.[3c]

We noted that the stereochemistry we were assigning at C7 (*S*)[4] of our synthetic structure was not the same as that assigned by the Pfizer discovery group to CP-263,114 (7*R*).[5, 6] However, one could not then be sure that the assignment to the natural product was necessarily correct. Some preliminary attempts on our part to epimerize aldehyde **3** were not successful and were attended by extensive decomposition. Accordingly, we undertook the installation of the remaining functionality required to go from **3** to the CP compounds (neglecting the issue of the C7 stereochemistry) in the hope of settling this question. Pentenylation of **3** followed by the oxidation of the resultant carbinol afforded **4** (Scheme 2).

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Fortunately, we could deprotect the primary hydroxyl group on the C4 side chain with dichlorodicyanobenzoquinone (DDQ) to afford alcohol **5**. Oxidation of **5** provided aldehyde **6**. The direct coupling of the compound with 1,1-diodoethane[7] gave rise to **7**. NMR spectral analysis continued to suggest that our compounds had the 7*S* configuration.[4, 8] At this stage we were in a position to exploit the fused 2-(*tert*-butyldimethylsilyl)furan moiety. Treatment of this compound, as previously described in our model studies[3b] indeed gave rise to the hemiacetal **8** as an anomeric mixture.[9] Oxidation with tetrapropylammonium perruthenate/*N*-methylmorpholine-*N*-oxide (TPAP/NMO) produced the internal carboxylic anhydride **9**.

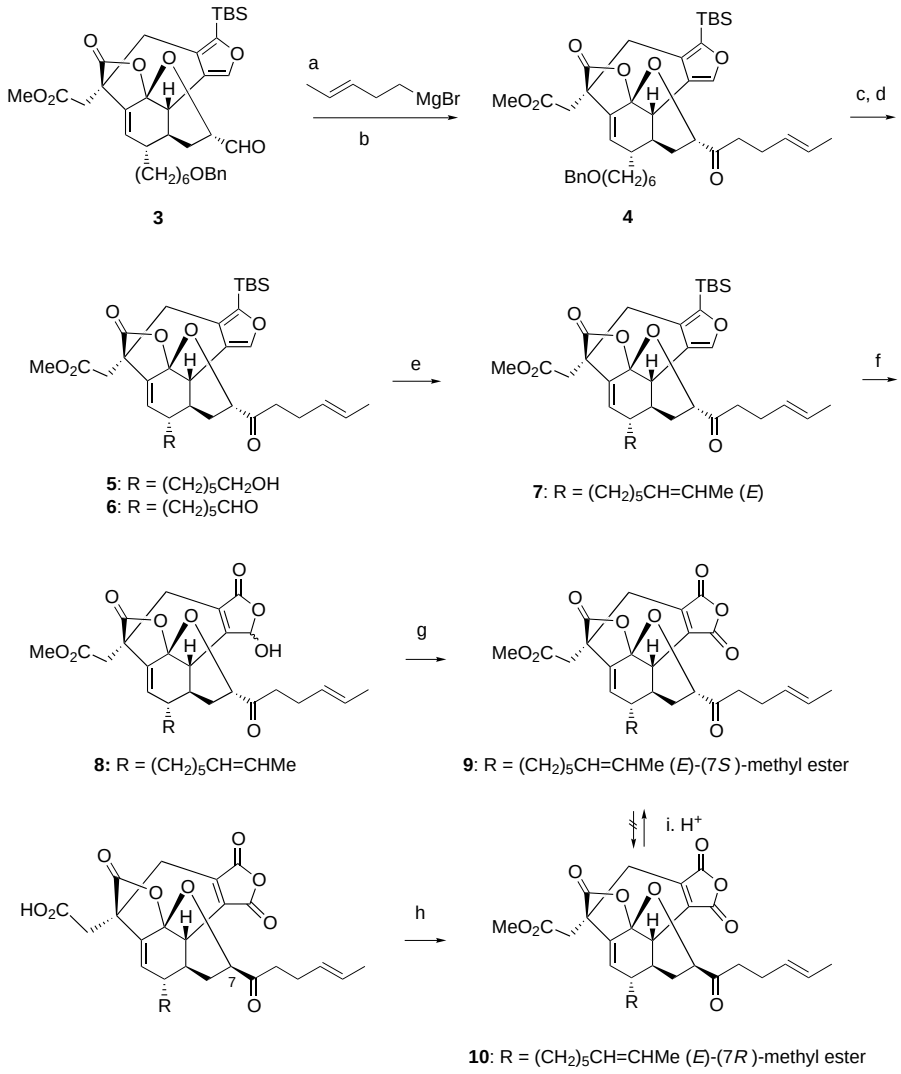
Definitive proof of the configuration of the natural series at C7[4] would require comparison with the methyl ester of CP-263,114, an unknown compound at the time. Of course, the obvious possibility of hydrolyzing **9** to its corresponding acid did not escape our attention. However, in practice, the attempted base-induced saponification of the methyl-ester linkage is superseded by other interesting chemistry (see below).

We were able to convert small reference samples of the acid **2**, made available to us from fermentation,[10] into its methyl ester through the action of diazomethane under carefully controlled conditions.[11] It was clear that the methyl ester **9**[12] obtained from synthesis was similar to, *but not the same as* that derived from **2**. Accordingly, we were obliged to conclude that the natural CP-derived ester indeed corresponds to structure **10**,[13] with the 7*R*[4] configuration in accordance with the assignment of Kaneko and colleagues.[5, 6] Correspondingly, the ester derived from total synthesis was, as we had surmised, **9** with 7*S* configuration.[3c]

At this point, we recorded a most surprising observation: following esterification of various trace specimens of **2**, provided by Pfizer scientists from various fermentation broths[10]—with **9** used as a reference sample—we could readily detect significant quantities (between 5 and 30%) of the synthetically derived 7*S* system **9** in addition to the major product **10**.[14] This finding raised the possibility that the 7S product may *also* be naturally occurring. We set this question aside and probed whether epimerization at C7 would be possible in the ester series. Interestingly, when a purified sample of **10**, prepared from the methylation of **2** with diazomethane, was subjected to the action of various strong acids such as trifluoroacetic acid (TFA) or, preferably methanesulfonic acid (MSA), there was clear epimerization at C7 leading to a mixture of **9** and **10**. With time, the mixture significantly favored **9**. A precise statement of the ratio is not possible, since some side reactions were occurring as "equilibration" was in progress. We note that after treatment with MSA for one week the ratio **9**:**10** is approximately 3:1. However, equilibrium had not yet been reached.

Unfortunately, attempted equilibration of **9** and **10**, starting with **9**, using TFA or MSA, was attended by serious decomposition in the case of the former acid and essentially no reaction with the latter reagent. These experiments show that the 7*S* compound, **9** is substantially more stable than the 7*R* compound **10** in the ester series.[4] More extensive investigations of the situation at C7 in the CP-225,917 series are described below.

While the full range of possible acid-catalyzed experiments or other epimerization strategies starting in the manifold of the "closed" 7-*epi*



Scheme 2. a) Diethyl ether, $-78\,^{\circ}C$ (80–90% conversion); b) Dess–Martin periodinane, CH_2Cl_2, 60% over two steps; c) DDQ, H_2O, CH_2Cl_2, 60%; d) Dess–Martin periodinane, CH_2Cl_2, 80%; e) 1,1-diiodoethane, $CrCl_2$, THF, 70%; f) *hv*, O_2, rose Bengal, *i*Pr_2EtN, CH_2Cl_2, $0\,^{\circ}C$; g) TPAP, NMO, CH_2Cl_2, ca. 50% over two steps; h) CH_2N_2, diethyl ether, >90%; i) CF_3COOH or $MeSO_2OH$, $CDCl_3$.

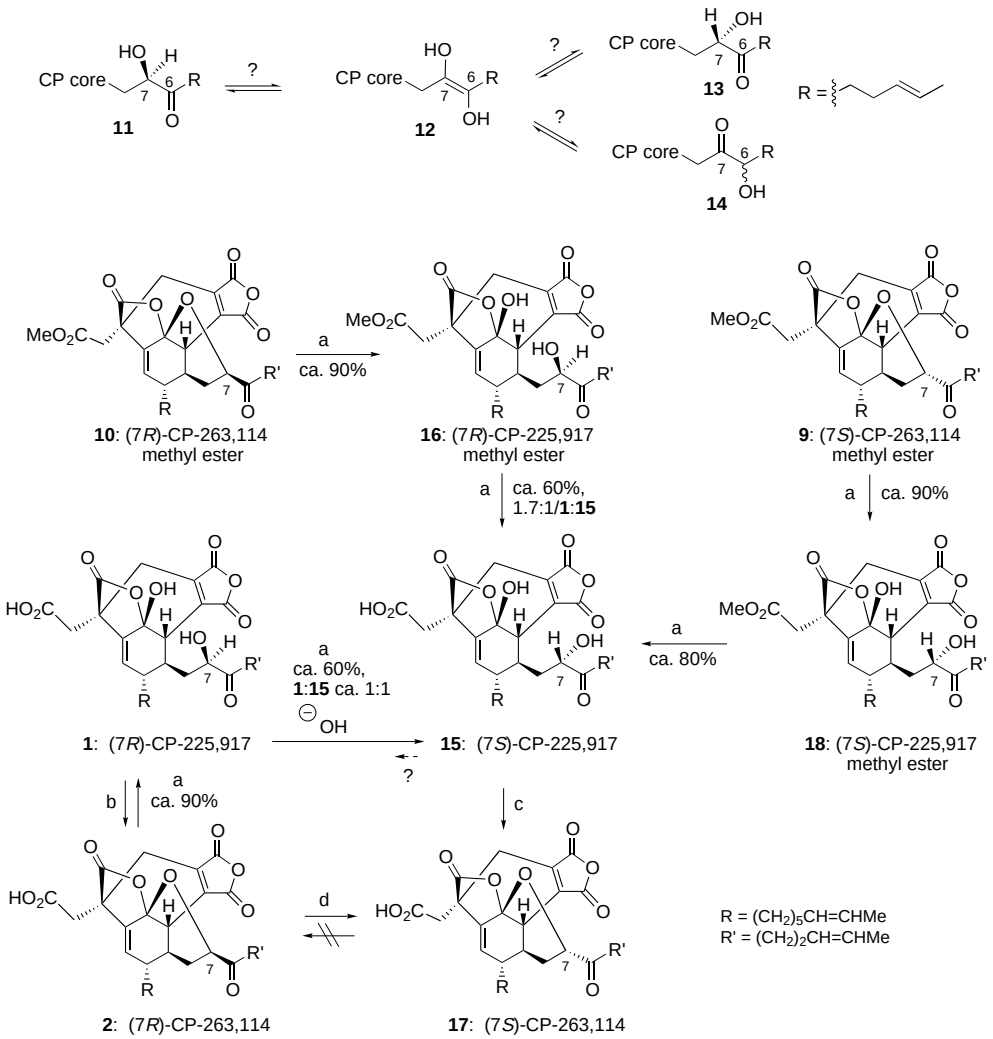
  1433-7851/99/3821-3198 $ 17.50+.50/0 *Angew. Chem. Int. Ed.* **1999**, *38*, No. 21

series has not yet been pursued, we posed the question as to whether base-catalyzed epimerization at C7 in the "open" CP series (see structure **1**; where "closed" and "open" refer to the presence and absence, respectively, of an ether bridge between C7 and C28) might be possible (Scheme 3). Such an epimerization could be pictured in terms of the C7-C8 enediols (see partial structure **12**). Clearly, this approach was not without its own attendant risks. In addition to C7 protonation to produce the two stereoisomeric alcohols at C7, there loomed the possibility that ketonization could occur at C7 (partial structure **14**), resulting in a new line of CP congeners that could not readily be "rehabilitated" in our total synthesis venture.

We first probed this question indirectly by starting with a specimen reference sample of the "open" CP acid **1**. In the event, treatment of this compound with lithium hydroxide, generated an approximate 1:1 mixture of **1** and a new acid **15**,[15] which we assumed to be the 7-epimer of **1**. Remarkably, the mixture seemed to be substantially confined to epimers at C7.[16] Thus, starting with **1**, crossing of the C7*R*–C7*S* boundary was possible without significant wandering into the structurally isomeric ketol terrain (→**14**).[16] The lithium hydroxide experiment was also conducted starting with the 7*R* methyl ester **10** of the natural series. The process was closely monitored by HPLC and ^{1}H NMR spectroscopy. The fastest step is that of cleavage of the δ-lactol, which is initiated by a reversible opening of the γ-lactone under formation of the open-chain methyl ester **16**. Concurrently, a slower epimerization at C7 was accompanied by hydrolysis of the methyl ester. After 24 h the ester linkage had been cleaved and the resultant mixture of acids, somewhat richer in **1** relative to **15**,[15] could be separated. Given the fact that the hydroxide-induced conversion of **10**→**16** occurs much more rapidly than hydrolysis of the ester, the critical role postulated by Nicolaou et al. of free carboxylate being a crucial element in a presumed "cascade" process to achieve the opening of the γ-lactone, as judged by cleavage of the δ-lactol, is open to considerable question.[2] In our case, clearly no such participation is involved in the hydroxide-driven opening of the γ-lactone since there are no free carboxylate groups.

Because of some attendant decomposition we cannot quote a precise equilibrium ratio of **1** and **15**. However, we were able to interconnect the open (CP-225,917) and closed (CP-263,114) systems in the 7*S* series by taking advantage of the cyclization reaction with methanesulfonic acid, initially discovered by the Pfizer scientists[6, 7] starting with the natural 7*R* isomer. Compound **1** was indeed converted into **2** exactly as they reported. Similarly, **15** was converted into **17**, the 7*S* analogue of **2.** In each case the cyclization reaction occurred without noticeable epimerization at C7. Long-term treatment of **2** with MSA did result in epimerization at C7. Thus, an 8:1 mixture of **17**:**2** was obtained from **2** after one week.[15, 16] Clearly, the 7*S* acid is substantially more stable than the 7*R* acid **2**, which is in keeping with our findings in the case of the corresponding esters **9** and **10**.

We now had in hand pure samples of the natural (7*R*) "open" (CP-225,917) and "closed" (CP-263,114) series as the acids (**1** and **2**) and the methyl esters (**10** and **16**), as well as the corresponding 7*S* series of closed acid (**17**), closed ester (**9**), open acid (**15**), and open methyl ester (**18**). At this point it was very clear that the reference samples of **2**, obtained from several fermentation runs, con-



Scheme 3. a) LiOH (0.1M):THF, 1:4; b) $MeSO_2OH$ (1 equiv), $CDCl_3$, ca. 90%; c) $MeSO_2OH$ (3 equiv), $CDCl_3$, ca. 90%; d) $MeSO_2OH$ (15 equiv), $CDCl_3$, ca. 90%, **17**:**2** = 8:1.

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tained between 5–30% of **17**. Without an authentic sample such as we had available through total synthesis, it would be quite understandable for the minor 7*S* version of **2** to be overlooked in an isolation program. We also note that the HPLC separation of **2** and its 7*S* epimer is quite difficult.[15]

We then explored the possibility of entering the natural series (7*R*) by base-catalyzed equilibration starting with the 7*S* epimers that could be derived from total synthesis. Remarkably, treatment of **15** with lithium hydroxide followed by acidification gave recovered starting material in addition to some general decomposition. At best, we could detect only trace quantities (about 5%) of **1** by HPLC. However, with the amounts of **15** available to us, fully homogenous CP-225,917 (**1**) was not secured from a total synthesis route.

In summary, the total syntheses of the 7*S*-CP systems has been accomplished. This program, initially directed at the total syntheses of **1** and **2**, has served to broaden our understanding of the chemistry of the CP-225,917 (open) and 263,114 (closed) series and to identify the 7*S* closed isomer **17** in the latter case as a very likely fermentation product. In the closed case a very powerful thermodynamic advantage favoring the 7-epi series (**9**/**10** and **17**/**2**) was discovered. We attribute this striking stability differential to the fact that in the epi series (**9** and **17**) the hexenoyl side chain projecting from C7 is *exo* with respect to the bicyclo-[3.3.1]nonane substructure. By contrast, in the naturally prevalent 7*R* series, the hexenoyl moiety is *endo* and substantially more hindered (Figure 1). A similar conclusion

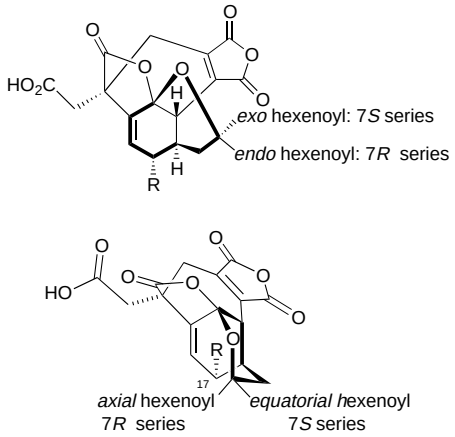

Figure 1. Positioning of the hexenoyl groups in the 7*R* and in the 7*S* series (for further information see the text).

arises from examining the two series from the sterical perspective of the tetrahydropyran ring. If this ring is in a chair conformation, then the hexenoyl group is equatorial in the 7*S* series while it is axial in the 7*R* case (Figure 1). Alternatively, the pyran ring may adapt an energetically costly boatlike conformation in the 7*R* case, to avoid placement of the large hexenoyl group in a 1,3-diaxial relationship to C17. In any case, dynamic equilibration apparently does not lead to detectable conversion of 7*S* into 7*R* diastereomer in the closed systems.

Surprisingly, the preference for the 7*S*-configured system, while perhaps less overwhelming, extends to the open CP-225,917 stereoisomers (**15** and **1**). Here it was initially felt that given free rotation in the open structures, the stability margins between the 7*R* and 7*S* isomers would have been markedly reduced. Instead, we again found (at least in the context of the systems where, in addition to the free $CH_2CO_2^-$, the internal anhydride has been opened to form a disodium salt) a strong preference for the 7*S* configuration. Apparently, even in the "open" series, there are rigidifying influences—possibly arising from intramolecular hydrogen bonds—which favor the 7*S* diastereomers. Whether the preference for the 7*S* configuration extends to "open" systems that lack the array of lithium carboxylates, remains to be established. Such matters, as well as the biological properties of the newly fashioned and recognized 7*S* compounds, are the subjects of continuing investigation.

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[4] Synthetic **3** is racemic. Furthermore, the absolute configuration of the natural products is not known. For purposes of discussion, we arbitrarily depict the absolute configuration as shown. The descriptors 7*R* or 7*S* is meaningful only in respect to the rest of the particular core structure enantiomer *drawn here*. We also note that in our earlier disclosure,[3c] this center (C7) had been numbered as C12 before the full construction of the CP system had been completed. We now return to the numbering system proposed by Kaneko et al.[5, 6]

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[7] T. Okazoe, K. Takai, K. Utimoto, *J. Am. Chem. Soc.* **1987**, *109*, 951.

[8] The NOESY spectrum of **3** showed a cross peak between H7 and H17 instead of the expected H7 and H10. Every "closed" compound with the 7*S* configuration at C7 exhibited a quartet at $\delta = 4.1-4.2$ in their ^{1}H NMR spectra. By contrast, 7R-CP-263,114 (**2**) and its methyl ester (**10**) display a triplet at $\delta = 4.5-4.6$ in the ^{1}H NMR spectra.

  1433-7851/99/3821-3200 $ 17.50+.50/0

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[10] The authors thank Dr. T. Kaneko and Dr. T. T. Dabrah of the Pfizer Central Research for providing a trace sample of natural CP-225,917 and several small samples of CP-263,114 from separate fermentation processes.

[11] Use of trimethylsilyldiazomethane leads to a trimethyl ester as the product from a ring opening of the anhydride. Some diazomethane methylations required 2-pentene as cosolvent to prevent side reactions at the two side-chain olefins.

[12] **9**: IR(film): $\tilde{\nu}=2921$, 1798, 1767, 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): $\delta=5.81$(s, 1H), 5.45–5.39 (m, 4H), 4.21 (dd, $J=12.2$, 3.0 Hz, 1H), 3.71 (s, 3H), 3.29 (s, 1H), 3.25 (d, $J=17.5$ Hz, 1H), 3.08 (d, $J=8.3$ Hz, 1H), 2.95 (d, $J=17.5$ Hz, 1H), 2.64 (dd, $J=19.2$, 2.2 Hz, 1H), 2.29–2.20 (m, 3H), 2.04–2.00 (m, 3H), 1.94–1.89 (m, 3H), 1.64–1.62 (m, 6H), 1.25–1.14 (m); HR-MS (FAB) calcd for $C_{32}H_{38}O_9Na$ $[M+Na]^+$: 589.2413, found: 589.2391.

[13] **10**: IR(film): $\tilde{\nu}=2927$, 1792, 1768, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): $\delta=5.66$ (d, $J=1.9$ Hz, 1H), 5.50–5.30 (m, 4H), 4.54 (t, $J=8.1$ Hz, 1H), 3.73 (s, 3H), 3.53 (s, 1H), 3.25 (d, $J=17.4$ Hz, 1H), 3.08 (d, $J=19.5$ Hz, 1H), 2.93 (d, $J=17.4$ Hz, 1H), 2.74–2.69 (m, 3H), 2.53 (m, 1H), 2.35–2.25 (m, 4H), 2.12 (dd, $J=13.6$, 8.8 Hz, 1H), 1.94–1.91 (m, 2H), 1.64–1.62 (m, 6H), 1.25–1.14 (m); HR-MS (FAB) calcd for $C_{32}H_{38}O_9Na$ $[M+Na]^+$: 589.2413, found: 589.2415.

[14] The trace fermentation acid samples came from several different sources which differed in the amount of the 7*S* system **17** (and subsequently its methyl ester **11**). The ratio of **2**:**17** did not change following storage of the samples in our premises for five months at $-78\,^{\circ}C$.

[15] Separation conditions of **1**, **2**, **15**, and **17:** Reversed-phase HPLC column: Metachem Inertsil 5 μ ODS2, 0.002 % H_3PO_4:CH_3CN = 4:6. Retention time: **15** (16 min), **1** (17 min), **2** (32 min), **17** (34 min). It is also crucial to inject the sample in a 1/1 mixture of 0.1 % H_3PO_4 in CH_3CN. We note also that the chromatography per se does not effect the homogeneity of the samples. Hence, we are confident that the 7*S* isomer we detected was present in the original samples.

[16] Another pathway not invoking enediol **12** would involve a reversible C6-C7 α-ketol shift with an intervening rotation about the C6-C7 σ bond. This step would effectively epimerize C7 without the necessary scrambling of the ketol. For this "ketol-shift" pathway, as well as the enediol pathway, to be viable, it would be crucial that the 7-hydroxy-6-ketone be much more stable than the 6-hydroxy-7-ketone isomers in both the 7*R* and 7*S* series.

[17] Dess–Martin periodinane: a) D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155; b) D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277; c) S. D. Meyer, S. L. Schreiber, *J. Org. Chem.* **1994**, *59*, 7549; d) R. E. Ireland, L. Liu, *J. Org. Chem.* **1993**, *58*, 2899; review of TPAP/NMO oxidation: S. V. Ley, J. Norman, W. P. Griffith, S. P. Marsden, *Synthesis* **1994**, 639.

Electron Microscopy Reveals the Nucleation Mechanism of Zeolite Y from Precursor Colloids**

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Zeolites are crystalline, porous solids whose intricate pore and channel systems in the molecular size range of 0.3 to about 1.5 nm are the basis for their immense importance in catalysis, separations, and ion exchange.[1–4] Although numerous studies have addressed the preparation of zeolites, it has been very difficult to model the complex mechanism by which they assemble from framework constituent precursor species under hydrothermal synthesis conditions.

An improved understanding of the synthesis mechanism is pivotal for the design of new zeolites (only about 100 structures are known so far), and for the preparation of novel zeolitic assemblies such as zeolite thin films for membrane reactors, monoliths, or functional nanostructures.[5] Here we report direct, high-resolution electron microscopic evidence for the nucleation mechanism of zeolite Y (faujasite structure type; FAU) in nanoscale amorphous aluminosilicate gel particles, followed by full conversion of the gel aggregates into 25–35 nm large single crystals of zeolite Y. Further crystallization of the colloidal zeolite Y suspension is mediated by soluble aluminosilicate species.

Different mechanisms have been discussed regarding nucleation and crystallization of zeolites, based on experimental evidence obtained with various methods such as X-ray diffraction and scattering, solid-state NMR spectroscopy, atomic force microscopy, and electron microscopy.[6–22] These include transformation of the precursor gel phase, aggregation and realignment of preassembled building blocks containing template molecule/(alumino)silicate clusters, and assembly of soluble small species from solution. Most of the above techniques give information about the final crystalline product; however, imaging the initial stage of zeolite formation has not previously been possible.

Several molecular sieves, including zeolite A, Y, L, ZSM-5, silicalite-1, TS-1, and $AlPO_4$-5 can be made in colloidal form with particle sizes in the nanometer range.[23–28] Recently, we reported a detailed study of the very early stages of zeolite A

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