[10] Abbreviations: H_2tmp: *meso*-tetrakis(2,4,6-trimethylphenyl)porphyrin, H_2(3,4,5-MeO-tpp): *meso*-tetrakis(3,4,5-trimethoxyphenyl)porphyrin, *m*-CPBA: *m*-chloroperoxybenzoic acid, H_2tpp: *meso*-tetraphenylporphyrin, H_2ttp: *meso*-tetrakis(*p*-tolyl)porphyrin, H_2tpfpp: *meso*-tetrakis(pentafluorophenyl)porphyrin, NBS: *N*-bromosuccinimide, Ts = *p*-toluenesulfonyl.

[11] a) J. T. Groves, R. Quinn, *J. Am. Chem. Soc.* **1985**, *107*, 5790; b) C. Ho, W.-H. Leung, C.-M. Che, *J. Chem. Soc. Dalton Trans.* **1991**, 2933.

[12] As tmp is a sterically encumbered porphyrin, whereas 3,4,5-MeO-tpp is basically a sterically unencumbered porphyrin ligand (the latter can not prevent formation of dinuclear μ-oxo ruthenium porphyrins), yet both of them gave nitrido ruthenium porphyrin **1** in similar yields, the steric properties of porphyrin ligands should have a minor effect on the $Ru\equiv N$ formation from reaction (2).

[13] The frequency of this new band is comparable to the $Ru\equiv N$ stretching frequency of 1023 cm^{-1} reported for the non-porphyrin nitrido ruthenium(VI) complex $[Ru^{VI}(N)Cl_3(AsPPh_3)_2]$ (a neutral, six-coordinate nitrido ruthenium(VI) species, like **1a** and **2**). See: D. Pawson, W. P. Griffith, *Inorg. Nucl. Chem. Lett.* **1974**, *10*, 253.

[14] CCDC-193042 (**1b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit @ccdc.cam.ac.uk).

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Synthesis of a marine macrolide

Stereocontrolled Total Synthesis of (+)-Leucascandrolide A**

Ian Paterson and Matthew Tudge*

Leucascandrolide A (**1**, Scheme 1) was isolated in 1996 from the calcareous sponge *Leucascandra caveolata*, collected off the east coast of New Caledonia, by Pietra and co-workers.[1] This polyoxygenated 18-membered macrolide features two trisubstituted tetrahydropyran rings, one of which has an unusual oxazole-bearing unsaturated side chain. To date, the true biosynthetic origin of this unique polyketide is uncertain.[2] Subsequent reisolation attempts proved unsuccessful which indicates that leucasandrolide A may be produced by opportunistic microbial colonization of the sponge.[2] Preliminary biological studies revealed potent cytotoxic activity against a range of cancer cell lines ($IC_{50} = 0.05$ and 0.25 μg mL^{-1} against KB oral epidermoid carcinoma and P388 leukemia cell lines, respectively), as well as pronounced antifungal activity. Since the natural supply of leucascandrolide A is unreliable, an efficient synthesis is paramount to enable further biological studies and, furthermore, to provide access to analogues. Consequently, leucascandrolide A has attracted considerable synthetic attention,[3–5] with the first total synthesis reported by Leighton and co-workers.[3] Herein, we report an expedient total synthesis of (+)-leucascandrolide A in which essentially complete control over all of the stereochemistry is achieved.

As outlined in Scheme 1, our approach relies on two Mitsunobu reactions—the first is employed to cyclize the *seco*-acid **2** and the second to append the heterocyclic side chain **3** at C5. A double Lindlar hydrogenation should then install the two *Z*-configured alkenes to provide leucascandrolide A directly. By exploiting the high degree of 1,3-dioxygenation embodied within the *seco*-acid **2**, we planned to introduce all the oxygenated stereocenters from tetrahydropyran **4** by using only substrate control. In light of the *anti* configurational relationship between C7 and C11, *seco*-acid **2** should be accessible from the β-oxygenated ketone **4** and aldehyde **5** by using our 1,5-*anti* aldol methodology.[5b,6,7] Furthermore, the resulting C11 stereocenter could then serve, in turn, to direct an alkylation with silyl enol ether **6** to install the full C15 side chain.

As shown in Scheme 2, the synthesis of the trisubstituted tetrahydropyran **4** began with a Jacobsen asymmetric hetero

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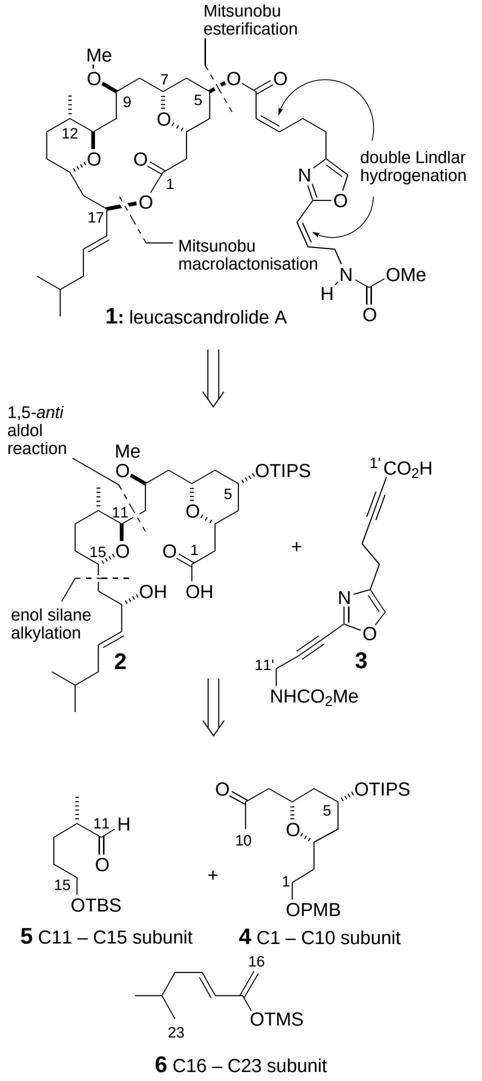
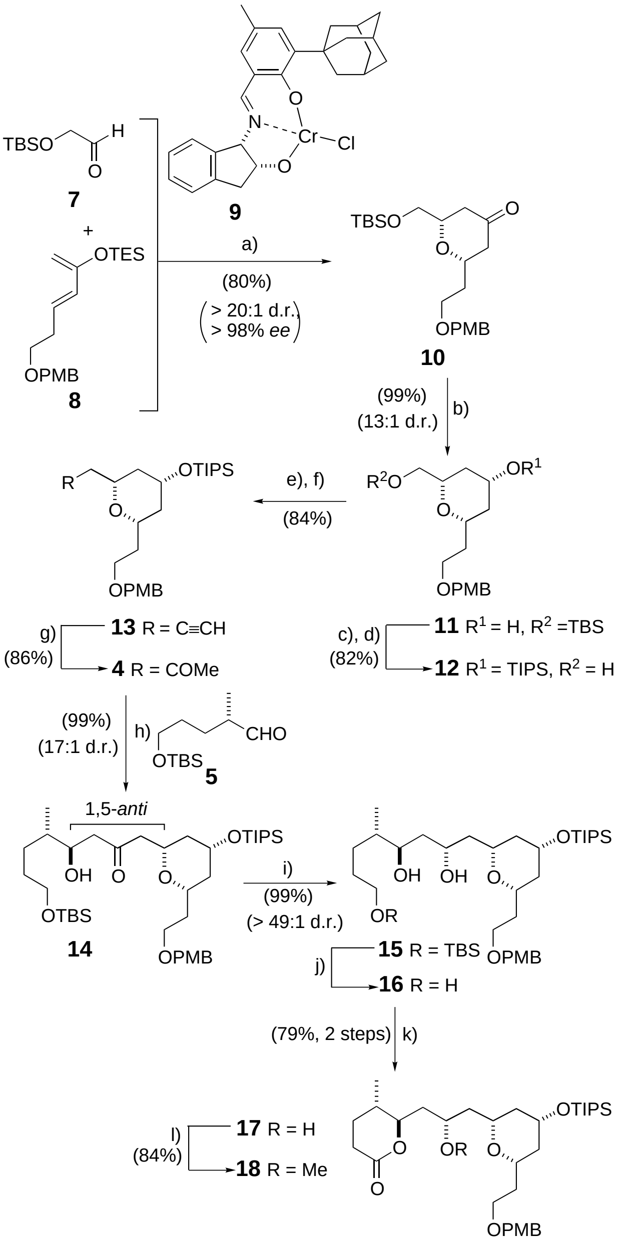


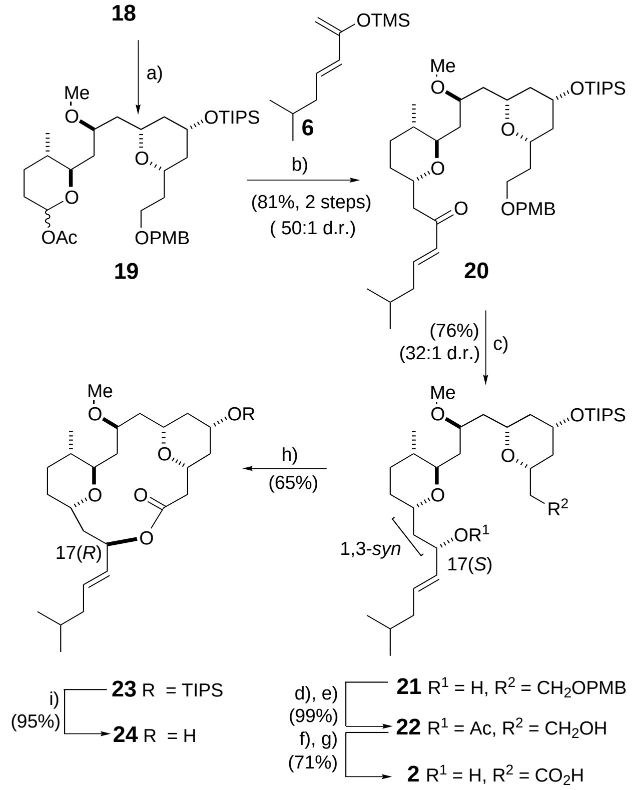
Scheme 1. Retrosynthesis of leucascandrolide A (**1**) leading to key building blocks **2**–**6**. TIPS = triisopropylsilyl; TBS = *tert*-butyldimethylsilyl; TMS = trimethylsilyl; PMB = *p*-methoxybenzyl.

Diels–Alder reaction of aldehyde **7** and readily available 2-siloxydiene **8**,[8] promoted by the chromium tridentate catalyst **9**.[9a] This generated the corresponding [4+2] cycloadduct,[9b] which, upon workup with mild acid, led to isolation of 2,6-*cis*-pyranone **10** in 80% yield with >20:1 d.r. and >98% *ee*. Installation of the equatorial C5 hydroxy group was achieved by treatment with $NaBH_4$ in MeOH to give secondary alcohol **11** in 99% yield and 13:1 d.r. Following TIPS ether formation, selective acidic removal of the TBS group gave primary alcohol **12** (82%). Homologation[10] to the methyl ketone **4** involved activation of alcohol **12** as its triflate derivative, displacement with lithium trimethylsilyl acetylide and basic methanolysis to give alkyne **13** (84%). Subsequent Hg^{II}-mediated hydration gave the methyl ketone **4** cleanly (86%). This efficient reaction sequence was performed to produce multigram quantities of enantiopure **4**.

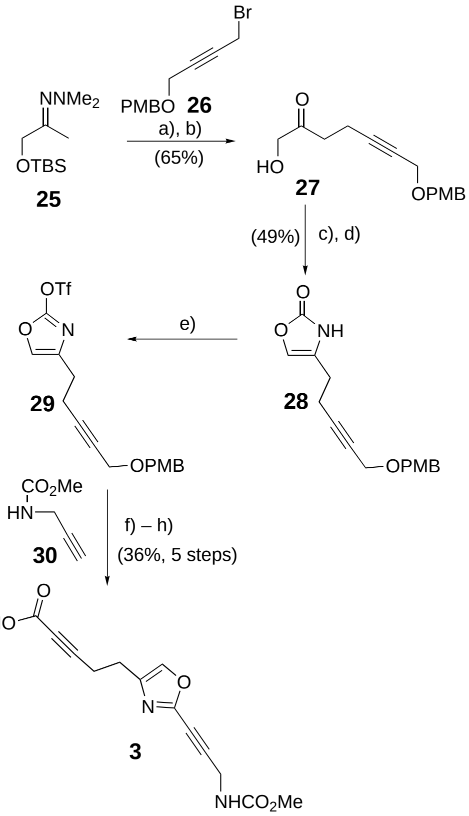
The key 1,5-*anti* aldol coupling reaction of β-alkoxy ketone **4** with aldehyde **5**[11] proceeded smoothly under our



Scheme 2. Preparation of advanced intermediate **18**. a) **9** (10 mol%), 4 Å molecular sieves, 20 °C, 20 h; acidified $CHCl_3$, 20 °C, 4 h; b) $NaBH_4$, MeOH, 20 °C, 2 h; c) TIPSOTf, lut, CH_2Cl_2, −78 °C, 2 h; d) CSA, 2:1 $MeOH/CH_2Cl_2$, 20 °C, 1 h; e) Tf_2O, pyr, CH_2Cl_2, −10 °C, 1 h; f) LDA, TMSC≡CH, HMPA, −78→20 °C, 1 h; K_2CO_3, MeOH, 20 °C, 12 h; g) cat. $Hg(OAc)_2$, PPTS, wet THF, 40 °C, 1 h; h) *c*Hex_2BCl, NEt_3, Et_2O, 0 °C, 30 min; **5**, −78 °C, 2 h; −78→−30 °C, 24 h; i) $Me_4NBH(OAc)_3$, 3:1 MeCN/AcOH, −40→−20 °C, 24 h; j) CSA, 2:1 $MeOH/CH_2Cl_2$, 25 °C, 1 h; k) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 20 °C, 12 h; l) Me_3OBF_4, proton sponge, CH_2Cl_2, 0→20 °C, 1 h. OTf = trifluoromeluoromethane sulfonate; lut = 2,6-lutidine; Tf_2O = trifluoromethane sulfonic anhydride; pyr = pyridine; LDA = lithium diisopropylamide; HMPA = hexamethyl phosphoramide; PPTS = pyridinium *p*-toluenesulfonate; CSA = 10-camphorsulfonic acid; TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxyl.



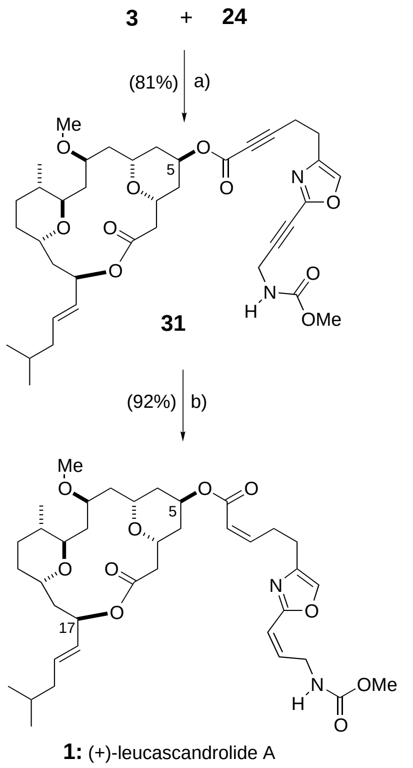
Scheme 3. Elaboration to the macrocyclic core **24**. a) DIBAL, CH_2Cl_2, then Ac_2O, pyr, DMAP, −78→−20 °C, 15 h; b) $ZnBr_2$, CH_2Cl_2, 20 °C, 4 h; c) $LiAlH(OtBu)_3$, CH_2Cl_2, −78→−10 °C, 1.5 h; d) Ac_2O, pyr, DMAP, CH_2Cl_2, 0→20 °C, 15 h; e) DDQ, 10:1 CH_2Cl_2/pH 7 buffer, 20 °C, 1 h; f) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 20 °C, 1 h; $NaClO_2$, $NaHPO_4$, methyl-2-butene, aq. *t*BuOH, 0→20 °C, 1 h; g) K_2CO_3, MeOH, 20 °C, 18 h; h) DEAD, PPh_3, PhH, 20 °C, 5 min; i) HF·pyr, THF, 0→20 °C, 5 h. DIBAL = diisobutylaluminum hydride; DMAP = 4-(dimethylamino)pyridine; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DEAD = diediethylazodicarboxylate.



Scheme 4. Preparation of the oxazole-bearing side chain **3**. a) LDA, HMPA, THF, −78→20 °C, 2 h; b) TBAF, THF, 20 °C, 1 h; c) $Cl_3CC(O)NCO$, CH_2Cl_2, 20 °C, 1 h; K_2CO_3, MeOH, 20 °C, 1 h; d) 4 Å molecular sieves, PhMe, 90 °C, 2 h; e) Tf_2O, lut, CH_2Cl_2, −78→−10 °C, 1 h; f) $[Pd(PPh_3)_4]$, **30**, lut, 1,4-dioxan, 20 °C, 6 h; g) DDQ, 10:1 CH_2Cl_2/pH 7 buffer, 20 °C, 1 h; h) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, 20 °C, 1 h; then $NaClO_2$, $NaHPO_4$, methyl-2-butene, aq. *t*BuOH, 0→20 °C, 1 h. TBAF = tetrabutylammonium fluoride.

standard conditions.[5b,6] Thus, treatment of **4** with *c*Hex_2BCl and Et_3N in Et_2O generated the corresponding less substituted enolate, which on addition of aldehyde **5** provided, after oxidative workup, aldol adduct **14** in 99 % yield and 17:1 d.r.[12] With the required 11*R* configuration installed, efforts were now focused towards constructing the second tetrahydropyran ring and installing the C9 stereocenter. To this end, 1,3-*anti* reduction of β-hydroxy ketone **14** with $Me_4NBH(OAc)_3$[13] provided diol **15** in 99 % yield and ≥50:1 d.r. Next, acidic removal of the TBS group gave triol **16**, which was oxidized selectively at the primary hydroxy group by using catalytic TEMPO and iodobenzene diacetate[14] to give δ-lactone **17** (79 %); by this procedure, the 1,5,7-triol was discriminated and the second pyran ring closed in a highly effective manner. This constitutes one of the first examples of a TEMPO-mediated procedure for achieving chemoselective lactone formation from open-chain polyols. Methylation of the isolated C9 hydroxy group with Me_3OBF_4 and proton sponge gave advanced intermediate **18** (84 %).

Effective anomeric allylation procedures for the stepwise installation of the C15 side chain have been reported by both Leighton et al.[3] and Rychnovsky et al.[4] In both these cases, however, following ozonolysis of the terminal alkene, the addition of either an alkenyl[3] or an alkynyl[4] organozinc to the derived aldehyde resulted in modest control over the C17 hydroxy stereocenter, that is, typically 3–3.5:1 in favor of the 1,3-*anti* stereochemistry (followed by a Yamaguchi macrolactonization). In contrast, we set about installing the full C16–C23 side chain with concomitant generation of the C15 stereocenter. As shown in Scheme 3, suitable activation of the anomeric position was achieved by treating δ-lactone **18** with DIBAL followed by in situ acetylation[15] to afford acetate **19**. Treatment of **19** with an excess of silyl enol ether **6**[16] in the presence of catalytic $ZnBr_2$[17] afforded ketone **20** cleanly in 81 % yield and ≥50:1 d.r. Next, a 1,3-*syn* reduction directed by the C15 pyran oxygen atom was envisioned to configure the C17 stereocenter ready for the planned Mitsunobu macrolactonization. Several reducing agents were screened in the presence of $ZnBr_2$ to induce metal chelation, but only $LiAlH(OtBu)_3$ provided a satisfactory selectivity (5:1 d.r.) in favor of the *syn* isomer. However, use of $LiAlH(OtBu)_3$ alone gave allylic alcohol **21** with much improved *syn* diastereose-



Scheme 5. Completion of the total synthesis of leucascandrolide A. a) DEAD, PPh$_3$, 1.5:1 THF/PhMe, 0→20 °C, 18 h; b) H_2, 5 % Pd/CaCO$_3$ poisoned with lead (Lindlar catalyst), quinoline, EtOAc, 20 °C, 2 h.

lectivity (76 %, > 32:1 d.r.) which indicates the operation of a nonchelation pathway possibly following the Evans polar model.[18] Acetylation of the resultant (17*S*)-hydroxy group followed by oxidative removal of the PMB group gave alcohol **22** in 99 % yield. Oxidation to the corresponding acid and saponification afforded *seco*-acid **2** (71 %) which set the stage for the Mitsunobu macrolactonization.[19] Pleasingly, treatment of **2** with DEAD and Ph$_3$P in degassed benzene for 5 min proceeded to give the desired macrocycle **23** in 65 % yield with clean inversion of configuration. Cleavage of the equatorial C5 TIPS ether was achieved by HF·pyr in THF to furnish macrocycle **24** in 95 % yield in readiness for the introduction of the axially oriented side chain at C5.

As shown in Scheme 4, preparation of the bis-alkyne side chain **3** relied on a Sonogashira coupling, in which the required oxazolyl triflate **29** was derived from alcohol **27**, the α-alkylation product of hydrazone **25**[20] and bromide **26**.[21] Treatment of **27** with trichloroacetyl isocyanate, followed by basic hydrolysis and heating the resulting intractable mixture to 90 °C, in the presence of 4 Å molecular sieves, produced the required oxazolone **28** (49 %). Reaction with triflic anhydride provided oxazolyl triflate **29** which was treated with alkyne **30**[3] under Sonogashira coupling conditions, as developed by Panek and co-workers,[22] to provide the side-chain precursor. Removal of the PMB group, followed by oxidation of the resulting alcohol to the carboxylic acid, then gave the required oxazole-bearing side chain **3**.

With the two key fragments in hand, we were now poised to test the Mitsunobu coupling on the equatorial C5 hydroxy group. As detailed in Scheme 5, reaction of acid **3** and macrocycle **24** in the presence of DEAD and PPh$_3$ in 1.5:1 PhMe/THF resulted in the smooth formation of the axial ester **31** in 81 % yield. Finally, Lindlar hydrogenation of the triple bonds enabled the stereospecific introduction of the two *Z*-alkenes to provide a 92 % yield of (+)-leucascandrolide A (**1**). This had spectroscopic data[23] in full accord with those reported by Leighton[3] and Pietra.[1]

In summary, we have completed a highly stereocontrolled synthesis of the potent cytotoxic macrolide leucascandrolide A, proceeding in 23 steps from **8** (longest linear sequence) and 5.3 % overall yield. Key features include a Jacobsen asymmetric hetero Diels-Alder reaction to configure the right-hand tetrahydropyran ring, a 1,5-*anti* aldol coupling, control over the C17 hydroxy center, and two sequential Mitsunobu reactions, to close the 18-membered macrolactone and append the oxazole-bearing side chain, respectively.

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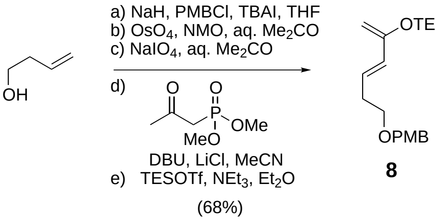

(1)

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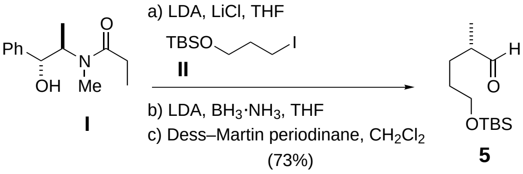

(2)

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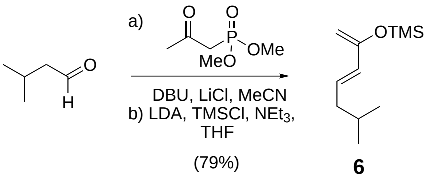

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Yttria-Zirconia Thin Films

Controlled Formation of Highly Ordered Cubic and Hexagonal Mesoporous Nanocrystalline Yttria–Zirconia and Ceria–Zirconia Thin Films Exhibiting High Thermal Stability**

Eduardo L. Crepaldi, Galo J. de A. A. Soler-Illia,
Anne Bouchara, David Grosso,
*Dominique Durand, and Clément Sanchez**

Zirconia-based mixed oxides are current targets of intensive research as a result of their applications in strategic technologies, such as yttria-stabilized zirconia (YSZ) in solid-oxide fuel cells (SOFCs),[1] and ceria–zirconia in the latest generation of automotive exhaust three-way catalysts,[2,3] the latter having the potential to be applied in the next generation of compact SOFCs.[3] In view of these applications, controlling the porosity of these systems is highly desirable. The "supramolecular template approach" offers precise control of the material porosity on the mesoscale (20–200 Å).[4] Ozin and co-workers[5] were the first to extend this method to the synthesis of YSZ by using cetyltrimethylammonium bromide (CTAB) templated glycolate-modified inorganic precursors. Gedanken and co-workers[6] reported the synthesis of mesoporous YSZ using metallic salts or oxides as inorganic sources and anionic surfactants as templates. All of these precipitation methods yield disordered wormlike mesoporous powders. However, to the best of our knowledge, periodically organized mesoporous ceria–zirconia and even yttria–zirconia materials are yet to be reported.

The present work reports the first examples of periodically organized mesoporous yttria–zirconia (YZ) and ceria–zirconia (CZ) ($R = \mathrm{M}/(\mathrm{M}+\mathrm{Z}) = 0.05$–$0.30$, where Z is the amount of Zr and M is the amount of Y or Ce present in the material). Moreover, these materials are processed as thin films. The procedure is simple and reproducibly gives highly ordered mesoporous nonsilicate mixed oxides, which retain their structure (order and porosity) after crystallization of the inorganic walls and subsequent thermal treatment to temperatures as high as 700 °C. This advantageous one-step method can replace the usual precipitation of particles/deposition/

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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