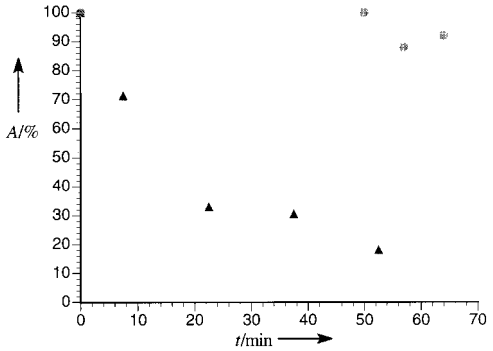

Figure 3. Influence of the chain transfer reagent **I** on the stability of the immobilized catalyst as determined from RCM experiments carried out with diethyldiallylmalonate with (●) and without (▲) CTA. A = Activity of the catalyst.

ture and the lack of basically any microporosity reduce diffusion to a minimum. This results in turnover frequences (TOFs) up to 25 min^{-1}, thus even exceeding homogeneous analogues. In comparison, the TOF for diethyldiethylmalonate using $[Cl_2Ru(Mes_2\text{-}NHC)(PCy_3)(CHPh)]$ is 4 min^{-1} (45 °C).[8]

In terms of a most simple handling, the monolithic systems presented here may be used either as pressure-stable reactors or (in miniaturized form) as cartridges for applications in combinatorial chemistry. The use of NHC ligands even in RCM successfully suppresses any bleeding of the column, thus allowing the synthesis of virtually ruthenium-free cyclization products with a ruthenium content ≤ 70 ppm.

Experimental Section

All experiments were carried out by means of Schlenk techniques using degassed and dried solvents throughout. Borosilicate columns (3×50 mm, 3×150 mm) were surface-derivatized using bicyclo[2.2.1]hept-2-en-5-yltrichlorosilane. Nitrogen and ruthenium contents were determined by elemental analysis and aqua regia decomposition followed by ICP, respectively. Molecular weights were determined by GPC (in THF) using a consecutive UV, refractive index (RI), and light scattering detectors.

Synthesis of monoliths: Solutions of A (NBE/DMN-H6/2-propanol, 25/25/40 wt%) and B (CH_2Cl_2/$[Cl_2Ru(=CHPh)(PCy_3)_2]$, 9.6/0.4)[22] were combined at 0 °C and the reaction mixture was transferred to a borosilicate column prechilled to 0 °C. Polymerization temperature was 0 °C for 15 min and room temperature for 1 h. For functionalization, the monolith was flushed with CH_2Cl_2 and subsequently fed with 2 mL of a solution of **1** (51.8 mg, 0.09 mmol) and norbornene (47.1 mg, 0.5 mmol) in CH_2Cl_2. Columns were closed and kept at 40 °C overnight. The monolith was flushed with CH_2Cl_2 (1 mL), a 10% solution of ethyl vinyl ether in CH_2Cl_2 (2 mL), and finally CH_2Cl_2 (2 mL) again. 4-Dimethylaminopyridine (10.9 mg, 0.09 mmol, dissolved in 1 mL CH_2Cl_2), CH_2Cl_2 (1 mL), and finally $[Cl_2(PCy_3)_2Ru(=CHPh)]$ (10.9 mg, 0.09 mmol, dissolved in 1 mL CH_2Cl_2) were pumped over the column which was then kept for 1 h. at 40 °C. Finally, the monolith was flushed with CH_2Cl_2 for a few hours at a flow rate of 0.1 mL min^{-1}. IGPC data (polystyrene, $M_p = 274$ Da, THF): specific surface area $\sigma = 25\ m^2 g^{-1}$, pore porosity $\varepsilon_p = 17\%$, intergranular porosity $\varepsilon_z = 40\%$, apparent density $\rho_{app} = 0.37\ g\,cm^{-3}$. Electron microscopy: microglobule diameter $d_p = 1.5 \pm 0.5$ μm.

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An Intramolecular Case of Sharpless Kinetic Resolution: Total Synthesis of Laulimalide**

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The Sharpless asymmetric epoxidation (SAE) is an efficient method for resolving racemic mixtures of secondary allylic alcohols: the matched pair of substrate and reagent generates an enantiomerically enriched epoxyalcohol, whereas the mismatched pair remains unreacted (Scheme 1, Eq. (1)).[1] We decided to change this intermolecular selection to an intramolecular one when we embarked on a total synthesis of

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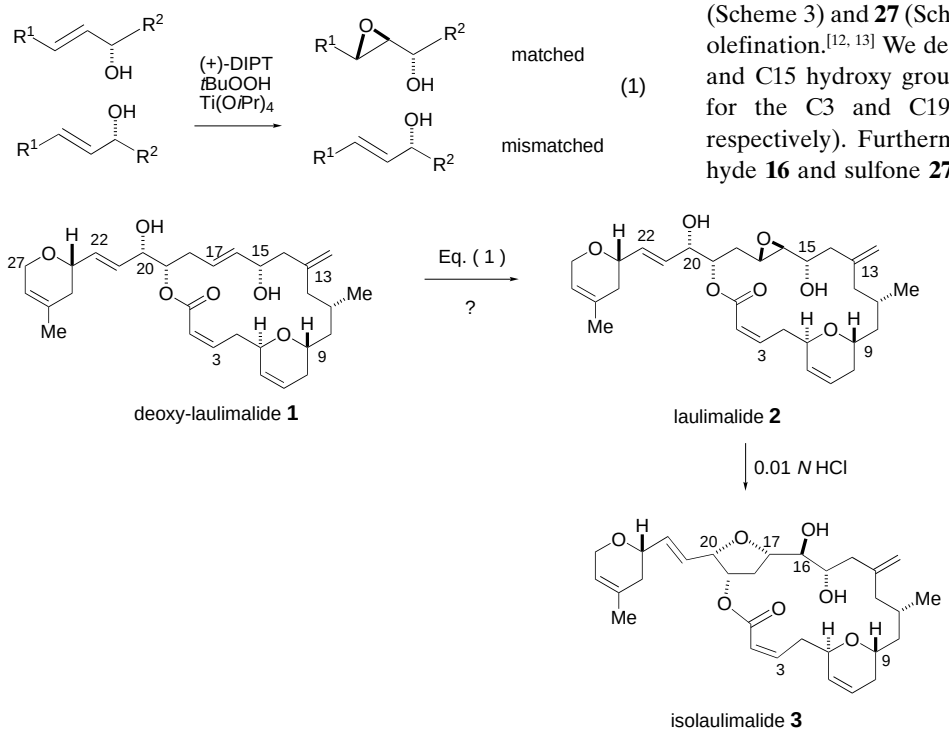


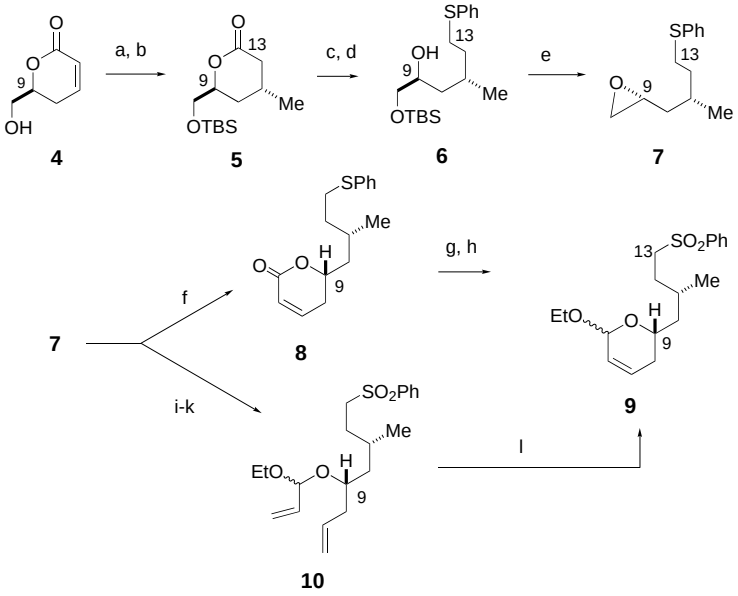
Scheme 1. The SAE route to laulimalide **2**.

the antitumor macrolide laulimalide (**2**). The last step of this synthesis was envisaged as the epoxidation of 16,17-deoxylaulimalide (**1**), in which the C15 – C17 section represents a matched and the C20 – C22 section a mismatched SAE situation with respect to Equation (1). This implies that **1** would be converted into **2** without the protection of the allylic alcohols. This strategy would be highly advantageous in view of the reported tendency of **2** to undergo cyclization to isolaulimalide (**3**), even under mildly acidic (and probably also basic) conditions,[2] which would place high demands on the removal of a protecting group from the C20 hydroxy group in the presence of the 16,17-epoxide.

The interest in a total synthesis of **2** has been kindled by the striking success of paclitaxel[3] as a novel drug against previously incurable tumors. However, in view of several problems associated with the clinical application of paclitaxel, a great deal of effort has been focused on the search for potential successors with the same mode of microtubule-stabilizing antitumor action, but with better bioavailability and higher activity against multidrug-resistant tumor cells. Among recent advances have been epothilone B and its derivatives,[4] discodermolide[5] and eleutherobin.[6] It was discovered quite recently that **2**, a metabolite from various marine sponges,[2, 7] also shows microtubule stabilization in eukaryotic cells and is distinguished by an unusually high antitumor activity against multidrug-resistant cell lines.[8] To date, only one total synthesis of **2** has been published,[9] along with several approaches to major fragments.[10]

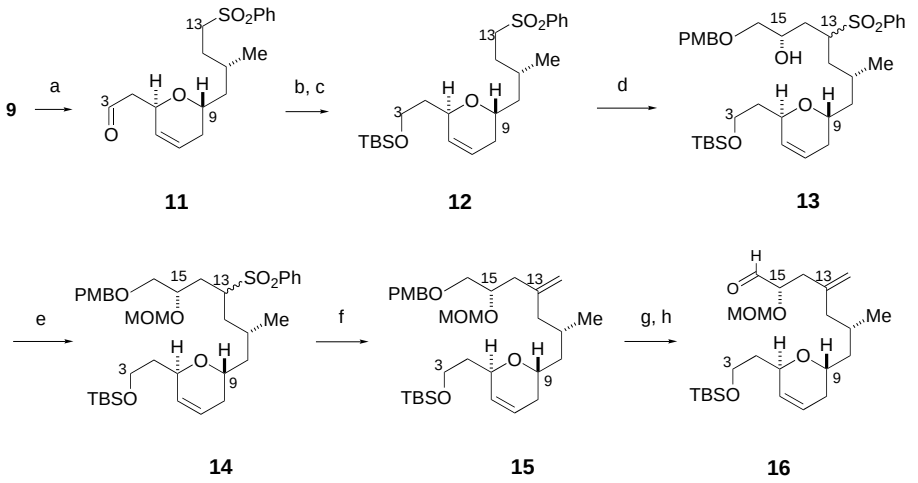
Retrosynthetically, we envisaged a Still – Gennari macrocyclization[11] of phosphonate aldehyde **29** (Scheme 6), which was expected to give 2,3-olefin with high *Z* selectivity. The *E* 16,17 olefin bond could be generated from fragments **16** (Scheme 3) and **27** (Scheme 5) by means of a Julia – Kocienski olefination.[12, 13] We decided to use MOM to protect the C20 and C15 hydroxy groups, and orthogonal protecting groups for the C3 and C19 hydroxy groups (TBS and PMB, respectively). Furthermore, we planned to synthesize aldehyde **16** and sulfone **27** from inexpensive chiral carbon pool compounds such as D-mannitol, (*S*)-malic acid, and D-glucose.

The synthesis of the C3 – C16 aldehyde **16** started from the known α,β-unsaturated lactone **4** (Scheme 2), which was readily available from tri-*O*-acetyl-D-glucal in four steps.[14] After conversion into the TBS derivative, addition of dimethyl copper lithium smoothly provided the desired 9,11-*trans*-disubstituted lactone **5** as a single diastereomer.[15] The formation of epoxide **7** required an inversion of the configuration at C9. Therefore, lactone **5** was reduced to the 1,5-diol, and the



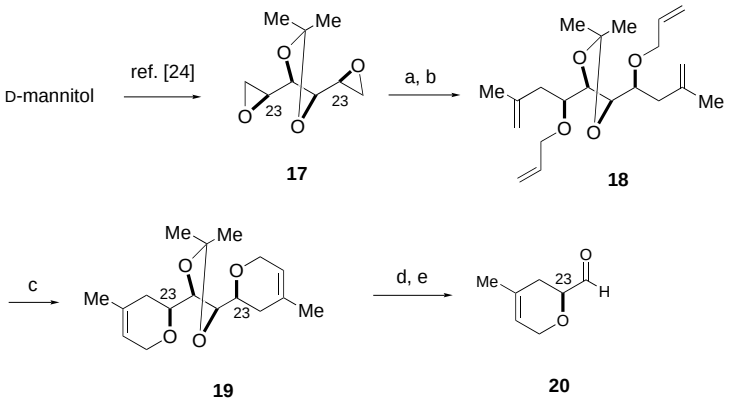
Scheme 2. Synthesis of **9**. Reagents and conditions: a) TBSCl, imidazole, DMAP, 5 °C to RT, 16 h, 89 %; b) Me_2CuLi (2 equiv), Et_2O, 0 °C, 1 h, 84 %; c) $LiBH_4$ (2.4 equiv), THF, 0 °C to RT, 17 h, 98 %; d) nBu_3P (2 equiv), $(PhS)_2$ (1.5 equiv), 0 °C to RT, 17 h, 83 %; e) 1. MsCl, Et_3N, CH_2Cl_2, – 10 °C to RT, 1 h; 2. TBAF, THF, 0 °C, 1 h, then aq. NaOH (15 %), 0 °C, 1 h, 89 %; f) 1. $PhSO_2(CH_2)_2C(OMe)_3$ (3 equiv), *n*BuLi, THF, – 78 °C, 30 min, then $BF_3 \cdot Et_2O$ (3 equiv) and **7**, – 78 °C, 1.5 h; 2. TFA/CH_2Cl_2 (9:1), RT, 3 h; 3) DBU (3.4 equiv), CH_2Cl_2, 0 °C, 30 min, 88 %; g) MMPP, EtOH, 10 °C, 1.5 h, 89 %; h) 1. DIBAL, (1.5 equiv), CH_2Cl_2, – 78 °C; 2) EtOH, PPTS, RT, 16 h, 93 %; i) MMPP, EtOH, RT, 2 h, 96 %; j) CH_2=CHMgBr (4 equiv), CuI (0.1 equiv), THF, – 40 °C, 30 min, 96 %; k) CH_2=CH–CH$(OEt)_2$ (20 equiv), PPTS, toluene, 35 to 40 °C, 80 mbar, 86 %; l) 1. $[(C_6H_{11})_3P]_2Cl_2Ru$=CHPh (5 mol %), CH_2Cl_2, 40 °C; 2. EtOH, PPTS, RT, 16 h, 90 %. TBS = *tert*-butyldimethylsilyl, DMAP = 4-dimethylaminopyridine, Ms = methanesulfonyl, TBAF = tetrabutylammonium fluoride, TFA = trifluoroacetic acid, DBU = 1,8-diazabicyclo(5,4,0)undec-7-ene, MMPP = magnesium salt of monoperoxyphthalic acid, DIBAL = diisobutylaluminium hydride, PPTS = pyridinium *p*-toluenesulfonate.

primary alcohol at C13 was selectively transformed into the corresponding phenyl sulfide **6**.[16] Mesylation of the C9 hydroxy group, desilylation, and ring closure with sodium hydroxide delivered epoxide **7**. Elaboration into the dihydropyran **9** was accomplished by means of ring-closing metathesis (RCM)[17] of diolefin **10**[18] as shown. A slightly higher overall yield was achieved by using Ghosez's one-pot lactonization[19] of **7** to give **9** via lactone **8** in 82% overall yield. The C3–C4 unit was stereoselectively introduced (Scheme 3) with vinyl *tert*-butyldimethylsilyl ether[20] to form aldehyde **11**, which was reduced with sodium borohydride and the resulting alcohol protected with a TBS group to give the C3–C13 fragment **12**. Compound **12** was converted into a 1:1 mixture of the C13-epimeric sulfones **13** by deprotonation and subsequent treatment with (*S*)-*p*-methoxybenzyl glycidyl ether.[21] The methylene group was introduced at C13 of MOM ether **14** by means of a Julia methylenation[22] to give **15**, which was transformed into aldehyde **16** by means of a two-step operation.



Scheme 3. Synthesis of **16**. Reagents and conditions: a) 1. CH_2=CHOTBS, (2 equiv), montmorillonite K10 clay, CH_2Cl_2, 0–5 °C, 45 min; 2. montmorillonite K10 clay, wet CH_2Cl_2, RT, 1.5 h; b) $NaBH_4$ (1.2 equiv), MeOH, 0 °C, 20 min, 86% over two steps; c) TBSCl, imidazole, DMAP, CH_2Cl_2, 0 °C to RT, 16 h, 98%; d) **12** (1.25 equiv), *n*BuLi, THF, −78 °C, 25 min, then $BF_3 \cdot Et_2O$, then (*S*)-*O*-PMB-glycidol, −78 °C, 2.5 h, 86%; e) MOMCl (10 equiv), Et*N*iPr_2 (20 equiv), CH_2Cl_2, 0 °C to RT, 24 h, 94%; f) *n*BuLi, THF/HMPA (10:1), −78 °C, 30 min, then ICH_2MgCl (5 equiv), −78 °C to −25 °C, 4 h, 75%; g) DDQ (1.5 equiv), CH_2Cl_2/pH 7 buffer (20:1), RT, 2.5 h, 81%; h) $(COCl)_2$ (1.5 equiv), DMSO (2.6 equiv), CH_2Cl_2, −78 °C, 3 min, then add alcohol, −78 °C, 30 min, Et*N*iPr_2 (5.2 equiv), −78 °C to RT, 45 min, 93%. MOM = methoxymethyl, HMPA = hexamethyl phosphoramide, PMB = *para*-methoxybenzyl, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Fragment **27** was prepared by means of an *E*-selective olefination of aldehyde **20** with phosphonate **23** and subsequent *syn*-selective reduction of the C20 carbonyl group (Scheme 5). The synthesis of **20** from (*R*)-glycidol by means of RCM has been reported independently by Ghosh[10c] and our group.[10g] In a novel approach (Scheme 4) we applied a bidirectional[23] RCM to tetraolefin **18**, which was readily prepared from the known D-mannitol-derived bis-epoxide **17** in two steps.[24] No RCM products were formed across the central acetonide ring,[25] which served as a barrier against cross-over metathesis.[26]



Scheme 4. Synthesis of **20**. Reagents and conditions: a) CH_2=CMeMgBr (4 equiv), CuI (0.4 equiv), THF, −40 °C, 2 h, 92%; b) 1. KO*t*Bu (3.5 equiv), THF, 45 °C, 1.5 h, 2. CH_2=$CHCH_2Br$ (4 equiv), RT, 17 h, 89%; c) $[(C_6H_{11})_3P]_2Cl_2Ru$=CHPh (3 mol%), CH_2Cl_2, RT, 5 h, 83%; d) TFA/CH_2Cl_2 (4:1), 0 °C, 3.5 h, 93%; e) HIO_4 (1.5 equiv), Et_2O, 0 °C to RT, 2 h, 95%.

The synthesis of β-oxophosphonate **23** (Scheme 5) started from the known butyrolactone **21**,[27] which was easily obtained from natural (*S*)-malic acid. Treatment of **21** with the lithium salt of diethyl methanephosphonate and subsequent deprotonation with one equivalent of lithium diisopropylamide[28] provided enolate **22**, which was silylated to give **23** after hydrolytic workup. Olefination[29] with aldehyde **20** afforded enone **24** stereoselectively and in high yield. Luche reduction[30] at −95 °C produced a 7.8:1 C20-epimeric mixture in favor of the desired epimer *syn*-**25**. After separation by HPLC (high-pressure liquid chromatography), the *anti* epimer was recycled by Parikh–Doering oxidation to give **24**.[31] Alcohol *syn*-**25** was converted into alcohol **26**, which was treated with 1-phenyl-1*H*-tetrazole-5-thiol under Mitsunobu conditions.[32] Oxidation of the resulting thioether[33] furnished the crystalline sulfone **27**.[34]

For the completion of the synthesis (Schemes 6 and 7), sulfone **27** and aldehyde **16** were connected by using a one-pot Julia–Kocienski olefination[12] to give olefin **28** as an 11.4:1 *E*/*Z* mixture from which (*E*)-**28** was isolated by chromatography. Deprotection of the C19 hydroxy group and acylation with bis(2,2,2-trifluoroethyl)phosphonoacetyl chloride,[35] followed by 3-O-desilylation and Dess–Martin oxidation[36] gave aldehyde **29**, which underwent cyclization under Still conditions[11] to furnish a 1.8:1 *E*/*Z* mixture[9a] of the macrolactones **30**. Separation of (*E*)- and (*Z*)-**30** by chromatography, followed by deprotection with dimethylboron bromide[37] generated the hitherto unknown deoxylaulimalides **1** and **31**, respectively. Exposure of **1** to SAE[38] with (+)-diisopropyl tartrate (DIPT) provided laulimalide (**2**).[39] Careful HPLC analysis revealed no other products, so that our initial strategy was successful. Admittedly, the regiocontrol of the epoxida-

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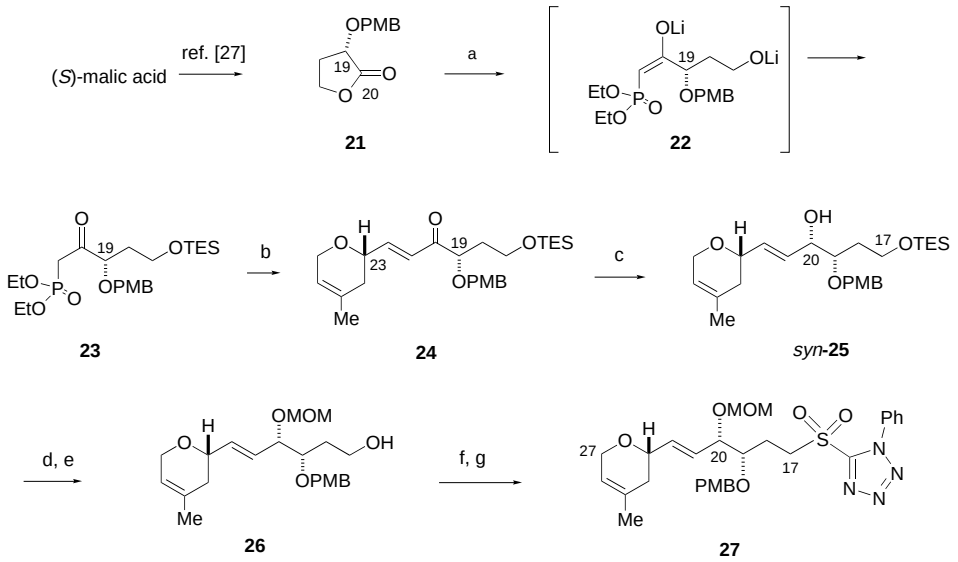

Scheme 5. Synthesis of **27**. Reagents and conditions: a) $MeP(O)(OEt)_2$ (1.0 equiv), *n*BuLi (1.0 equiv), THF, −78 °C, 15 min, then **21**, −78 °C, 30 min, then LDA (1.0 equiv), −78 °C, 30 min, then TESCl (2.0 equiv), −78 °C to RT, 16 h, 83 %; b) LiCl (2.5 equiv), Et_3N (2.5 equiv), THF, 0 °C, 10 min, then **20**, 0 °C, 2 h, 86 %; c) 1. $CeCl_3 \cdot 7H_2O$ (1.5 equiv), $NaBH_4$ (1.2 equiv), MeOH, −95 °C, 75 min; 2. HPLC separation (*syn*-**25**: 85 %, *anti*-**25**: 11 %); d) MOMCl (5 equiv), $EtN(iPr)_2$ (10 equiv), CH_2Cl_2, 0 °C to RT, 24 h; e) TBAF, THF, RT, 15 min, 93 % over two steps; f) PPh_3 (1.5 equiv), 1-phenyl-1*H*-tetrazole-5-thiol (1.5 equiv), DEAD (1.8 equiv), THF, 0 °C, 30 min, 90 %; g) $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$, H_2O_2 (30 %), 0 °C to RT, 74 %. LDA = lithium diisopropylamide, TES = triethylsilyl, DEAD = diethyl azodicarboxylate.

tion could also be the result of a substrate effect. Kinetic resolution can only be proved unambiguously by the (−)-DIPT-mediated reaction of **1**, which has not yet been carried out owing to insufficient material.

In conclusion we have presented a total synthesis of **2** (the longest linear sequence has 24 steps) and two deoxy derivatives (**1** and **31**) which is convergent and stereocontrolled except for the ring-closing Still–Gennari olefination. Work is underway in our laboratory to substitute this step by novel *Z*-specific ring-closing C–C connections (for an alternative, see ref. [9b]). Nevertheless, the modular character of the approach allows the design of a variety of suitable derivatives.

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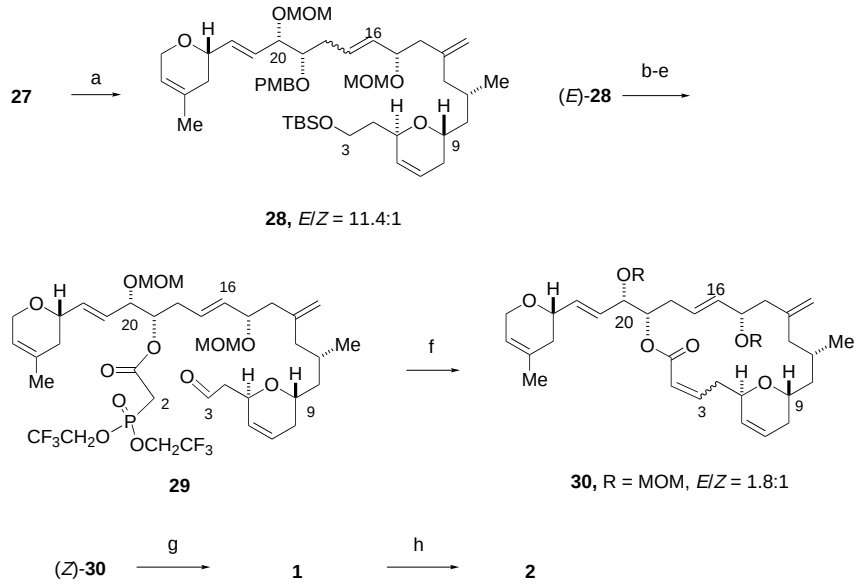
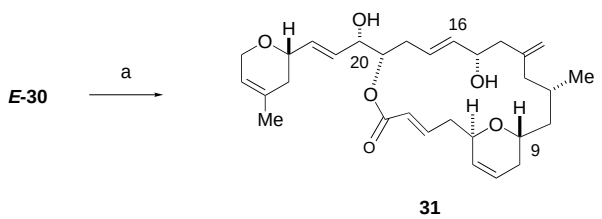


Scheme 6. Completion of the synthesis of **1** and **2**. a) KHDMS, DME, −60 °C, 25 min, then **16** (1.15 equiv), −60 °C to RT, 4 h (57 % (*E*)-**28** + 5 % (*Z*)-**28**); b) DDQ, CH_2Cl_2/pH 7 buffer (10:1), RT, 50 min, 87 %; c) $(CF_3CH_2O)_2P(O)CH_2COCl$ (3.5 equiv), DMAP (3.5 equiv), CH_2Cl_2, −78 °C, 10 min, then pyridine, −78 °C to RT, 45 min, 91 %; d) AcOH/H_2O/THF (3:1:1), 3.5 h, RT, 89 %; e) Dess–Martin periodinane (2.5 equiv), wet CH_2Cl_2, RT, 30 min, 96 %; f) **29** (10^{-3} M in THF), [18]crown-6 (6 equiv), −78 °C, then KHDMS (0.95 equiv), −78 °C, 50 min, 80 %; g) 1. Me_2BBr (6 equiv), CH_2Cl_2, −78 °C, 25 min; 2. aq. $NaHCO_3$/THF (1:2), 80 %; h) (+)-DIPT (1.2 equiv), $Ti(OiPr)_4$ (1.0 equiv), *t*BuOOH (1.34 equiv), 4-Å molecular sieves, −20 °C, 2 h: 70 % (**2**) and 30 % (**1**; recovered). KHDMS = potassium 1,1,1,3,3,3-hexamethyldisilazane, DME = 1,2-dimethoxyethane.



Scheme 7. Synthesis of **31**: a) 1. Me_2BBr (6 equiv), CH_2Cl_2, −78 °C, 25 min; 2. aq. $NaHCO_3$/THF (1:2), 84 %.

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Methylenetriimidosulfate $H_2CS(NtBu)_3^{2-}$—The First Dianionic Sulfur(VI) Ylide**

Bernhard Walfort and Dietmar Stalke*

Isoelectronic replacement of the oxygen atoms in simple p-block element oxoanions by an NR imido group is currently a flourishing area of main group chemistry.[1] These new species are soluble in nonpolar organic solvents because they form contact-ion pairs, whose periphery consists of lipophilic substituents. In contrast, the simple oxoanions form infinite solid-state lattices as a result of the multiple oxygen – metal cation contacts. We were particularly interested in the polyimidosulfur anions because of the rich redox chemistry.[2]

Triimidosulfite $S(NR)_3^{2-}$,[3] which is analoguous to sulfite SO_3^{2-}, can be radically oxidized to $S(NR)_3$ (Scheme 1).[4] The cap-shaped $S(NR)_3^{2-}$ ion is the first tripodal coordinating dianion.[5] Tetraimidosulfate $S(NR)_4^{2-}$, which is analogous to sulfate SO_4^{2-}, [6] gives soluble monomeric metal complexes.[7]

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