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Concise Enantioselective Synthesis of the Ten-Membered Lactone Cephalosporolide G and Its C-3 Epimer

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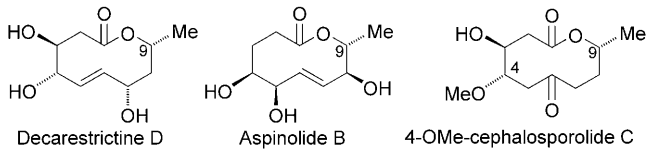
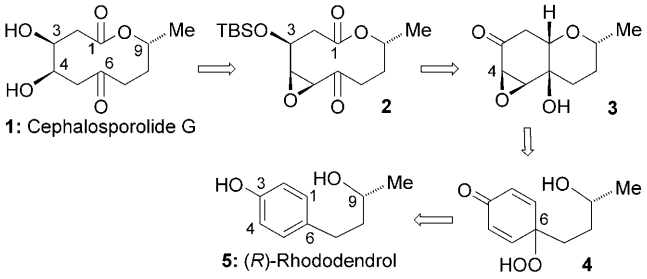
Among the naturally occurring lactones of ring sizes in the range of eight to eleven,[1] the ten-membered lactones, also called decanolides, are the most abundant and biologically active.[2] This family of natural products displays a wide range of biological properties, such as antibacterial and antifungal activity and the inhibition of cholesterol biosynthesis.[2a] Besides the macrolactone core, they share a methyl group at C-9, but differ in the number and nature of oxygen functionalities and the degree of unsaturation (Scheme 1).



Scheme 1. Examples of naturally occurring ten-membered lactones.

Concerning synthetic studies, the main challenge has been the efficient construction of the medium-sized ring, since cyclisations of acyclic precursors are difficult due to enthalpy and entropy factors.[3] The two major approaches involved the intramolecular lactonisation of activated hydroxyacids,[4] mainly by using the method developed by Yamaguchi, which generally proceeded in moderate yields[5] and the ring-closing metathesis[6] of acyclic olefins, which is still limited in scope because the control of *E*/*Z* stereochemistry of the double bond generated is difficult and because of the low reactivity of the acyclic precursor when dense functionality close to the reaction centre exists.[7] Moreover, the use of the chiral pool for the asymmetric preparation of key intermediates in the synthesis of natural decanolides requires a large number of hydroxy group protections and deprotections, making the synthetic sequences lengthy and very expensive.[8] For these reasons, there is a need for methodologies that allow for high-yielding construction of the macrolactone ring and new strategies to develop short, atom-economic approaches to naturally occurring decanolides.

Cephalosporolide G (**1**; Scheme 2) was isolated in 1995 from the fungus *Cephalosporium aphidicola*,[9a] the absolute configuration and specific rotation of which were not reported by the authors. Until very recently, none of the members of the cephalosporolides,[9] a subfamily within the decanolides, had been synthesised. In 2008, Krishna and Sreeshailam reported the first total synthesis of 4-OMe-cephalosporolide C (Scheme 1) from L-malic acid and (2*R*)-2,3-*O*-cyclohexylideneglyceraldehyde in a lengthy 20-step reaction sequence, including three hydroxy group protection–deprotection steps, and a Yamaguchi macrolactonisation (48% yield) for the key construction of the 10-membered ring.[10]



Scheme 2. Retrosynthetic analysis of **1**.

Herein, we describe the first enantioselective synthesis of the natural decanolide **1** and its C-3 epimer in only eight and seven steps, respectively, starting from the natural phenol (*R*)-rhododendrol (**5**). Our strategy features three highly selective oxidations to introduce the oxygenated functionality at the C-1, C-4 and C-6 positions of the natural product and the whole carbon skeleton is already present in the starting material. Moreover, the key formation of the

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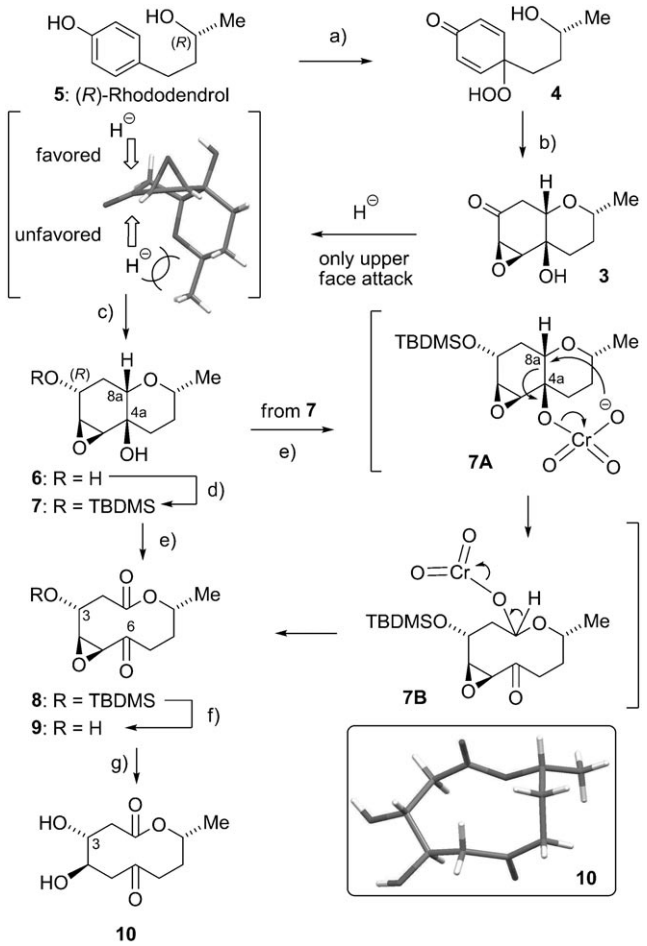
macrolactone ring is carried out by the use of a high-yielding pyridinium chlorochromate (PCC)-mediated oxidative cleavage of a bicyclic intermediate, generated in a domino sequence from a *p*-peroxyquinol.

The retrosynthetic analysis of **1** from **5** is shown in Scheme 2. Decanolide **1** could be synthesised by silyl deprotection and regioselective reductive opening of epoxide **2**, which could be prepared from the bicyclic derivative **3** by stereoselective carbonyl reduction and a controlled oxidative cleavage–ring-expansion process to generate the macrolactone. Compound **3**, in turn, could be formed by a stereocontrolled conjugate cyclisation/intramolecular epoxidation of the peroxyquinol **4**, which is easily available by oxidative dearomatisation of **5**. All of the carbon atoms in the final target **1** can be recognised in the *p*-alkyl-substituted phenol **5**.

As depicted in Scheme 3, we started the synthesis with (−)-rhododendrol (*R*)-**5** (>99% enantiomeric excess (*ee*)), which was obtained by enzymatic resolution of the racemic



Scheme 3. Total synthesis of 3-epi-cephalosporolide G (**10**) (7 steps, 15.2% overall yield). a) Oxone, $NaHCO_3$, H_2O/CH_3CN, RT, 1 h, 65%; b) i) *p*-TsOH (0.12 equiv), $CHCl_3$, −20°C, 3.5 h; ii) triton B (0.24 equiv), $CHCl_3$, RT, 4 h, 49%; c) $NaBH_4$, EtOH, RT, 1.5 h, 96%; d) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C to RT, 30 min, 95%; e) PCC, NaOAc, CH_2Cl_2, RT, 1 h, 68%; f) Pyr·HF, CH_3CN, 0°C to RT, 2 h, 81%; g) Al (Hg), THF/EtOH/H_2O, RT, 95%.

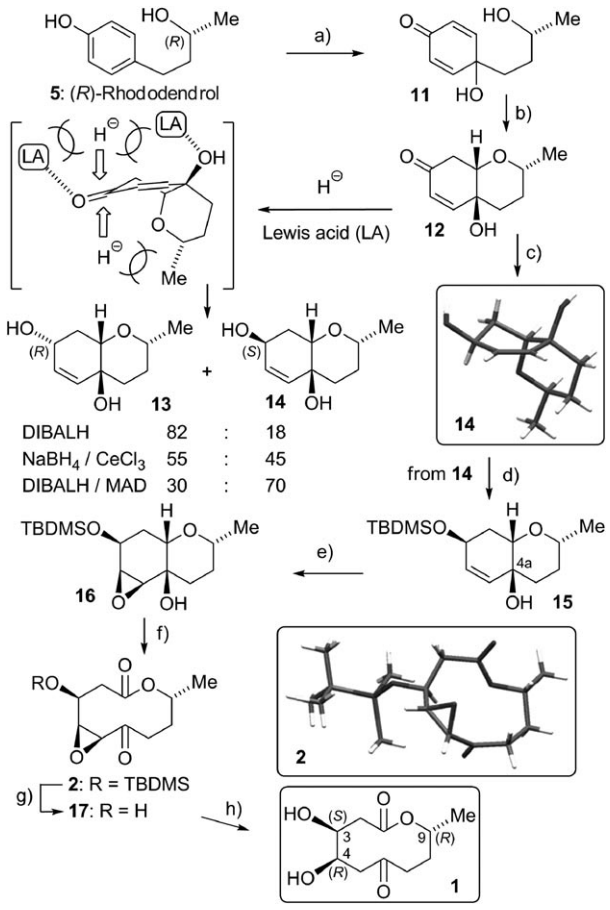
derivative.[11] We submitted phenol (*R*)-**5** to an oxidative dearomatisation process with singlet oxygen, generated from Oxone in the presence of $NaHCO_3$,[12] to afford **4**, in 65% yield. The treatment of compound **4** with *para*-toluene sulfonic acid (*p*-TsOH; 0.12 equiv) followed by Triton B (0.24 equiv) gave, in one step and 49% yield, the tricyclic epoxide **3**. The formation of **3** occurred in an efficient catalytic tandem process[13] beginning with the acid-catalysed conjugate addition of the secondary OH to one of the double bonds of the cyclohexadienone moiety of **4**, followed by the base-catalysed epoxidation of the other double bond of the molecule by the hydroperoxy group acting as an intramolecular epoxidation reagent. The whole sequence occurred in a highly chemo- and diastereoselective manner leading to the exclusive formation of **3**.

The original plan to access **1** included the reduction of the carbonyl group of **3** to the corresponding *S*-carbinol to install the correct stereochemistry present at C-3 in the natural product (Scheme 3). Nevertheless, the reduction of ketone **3** with $NaBH_4$ exclusively afforded the alcohol (*R*)-**6** in 96% yield. Reaction of **3** with diisobutylaluminum hydride (DIBAL-H) or the bulky hydride L-Selectride also occurred in a highly stereoselective manner to afford the same *R*-configured carbinol **6** as the only detected isomer. The origin of this stereoselectivity could be found in the structure of the *cis*-fused bicyclic derivative **3**, in which only the upper convex face of the carbonyl group is available for the hydride approach (Scheme 3).

In view of this result, we decided to continue the synthesis of the C-3 epimer of the natural cephalosporolide G to validate our initially proposed strategy. After protection of the secondary carbinol of compound **6** as the *tert*-butyldimethylsilyl (TBDMS) derivative **7** (TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 95%, OTf = trifluoromethanesulfonate), we undertook the key step, which was the formation of the 6-keto 10-membered lactone moiety by an oxidative cleavage of the C-4a–C-8a bond of the tricyclic epoxide **7** (Scheme 3). Initially, we made several attempts with oxidants, such as $RuCl_3/NaIO_4$,[14] phenyliodonium(III) diacetate (PIDA)/I_2[15] or PIDA/I_2 followed by *meta*-chloroperbenzoic acid (*m*CPBA)/$BF_3{\cdot}OEt_2$/pyridine (Pyr),[16] previously used for similar substrates. Nevertheless, these methods gave complex reaction mixtures in which the products of oxidation at different positions could be detected showing an evident lack of selectivity. To our delight, we found that PCC in the presence of NaOAc (RT, 1 h), cleanly and selectively oxidised compound **7** to the 6-keto decanolide **8**, with a remarkable 68% yield after chromatographic purification. The initial reaction of the tertiary alcohol at C-4a of **7** with PCC would form the corresponding chromate intermediate **7A**, which could then initiate an intramolecular oxidation at C-8a and fragmentation of the C-4a–C-8a single bond, with concomitant oxidation of the carbinol at C-8a to the corresponding ketone, to afford the 10-membered ring lactol **7B**. Finally, elimination of the *ipso* proton and reduction of the chromium unit would give the required 6-keto 10-membered lactone **8**.

With decanolide **8** in hand, we recovered the free carbinol at C-3 by treatment with HF·Pyr to afford alcohol **9** in 81% yield. Finally, regioselective opening of the epoxide ring of **9** with sodium amalgam[17] gave, in 95% yield, compound **10**, which is the C-3 epimer of the naturally occurring decanolide **1**. The ten-membered lactone structure, as well as the correct configuration of the stereogenic centres of **10**, was demonstrated by X-ray analysis.[18] Thus, we have described the total synthesis of **10** in only 7 steps from (*R*)-rhododendrol (**5**), in 15.2% overall yield.

Having established the viability of our approach to the highly functionalised ten-membered lactone core of cephalosporolides, we turned our attention to the preparation of a precursor of the natural product **1** with the correct *S* absolute configuration at the C-3 position. Taking into account the observed stereochemical course in the reduction of the epoxy ketone **3** (Scheme 3), we decided to evaluate the behaviour, in the reduction step, of a similar bicyclic ketone, such as **12** (Scheme 4), which lacks the epoxide ring. The synthesis of **12** started with treatment of **5** with Oxone in the presence of $NaHCO_3$, followed by the in situ addition of a reductant such as $Na_2S_2O_3$, affording the *p*-quinol **11** in 53% yield. The efficient differentiation of the two diastereotopic faces and the two diastereotopic double bonds of the cyclohexadienone moiety of **11** could be achieved by a stereoselective (95:5 dr) conjugate addition of the secondary OH of the hydroxybutyl chain at C-4 to one of the double bonds of **11**, promoted by a catalytic amount of *p*-TsOH. The bicyclic, *cis*-fused α,β-unsaturated ketone **12** was thus isolated in 79% yield. In this case, the addition of a small hydride source, such as DIBAL-H, to ketone **12** afforded an 82:18 mixture of alcohols (*R*)-**13** and (*S*)-**14**; this is the first time that attack on the lower face has been observed, albeit in a very poor ratio. At this point, we reasoned that the addition of a bulky Lewis acid, prior to the addition of the hydride, could modify this stereochemical behaviour because the initial coordination to the carbonyl group and/or the free OH would preferentially take place from the less encumbered upper face of ketone **12**, thus hindering the hydride approach and possibly favouring the desired lower-face hydride attack (Scheme 4). Indeed, when we submitted ketone **12** to reduction with $NaBH_4$ in the presence of $CeCl_3·7H_2O$, a 55:45 mixture of carbinols (*R*)-**13** and (*S*)-**14** was obtained, the required lower-face attack still being the minor one. Pleasingly, the reaction of compound **12** with DIBAL-H in the presence of the exceptionally bulky Lewis acidic reagent methyl aluminium bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD)[19] gave rise to a 30:70 mixture of alcohols (*R*)-**13** and (*S*)-**14**, from which the desired diastereoisomer (*S*)-**14** could be isolated in pure form with a remarkable 65% yield after chromatographic separation. The exact structure of the bicyclic carbinol (*S*)-**14** could be secured by X-ray analysis.[18] It is worth mentioning that when we tried the reduction of epoxy ketone **3** (Scheme 3) in the presence of $CeCl_3·7H_2O$ or MAD, again carbinol (*R*)-**6**, resulting from upper-face attack, could be detected as the only reaction product.



Scheme 4. Total synthesis of cephalosporolide G (**1**) (8 steps, 12.9% overall yield). a) i) Oxone, $NaHCO_3$, H_2O/CH_3CN, RT, 1 h; ii) $Na_2S_2O_3$, RT, 5 min, 53%; b) *p*-TsOH (0.12 equiv), $CHCl_3$, −20°C, 3.5 h, 79%; c) MAD, 0°C, 1 h, then DIBAL-H, −78°C, 14 h, 65%; d) TBDMSCl, imidazole, DMAP, CH_2Cl_2, RT, 3 h, 96%; e) *m*CPBA, CH_2Cl_2, RT, 14 h, 93%; f) PCC, NaOAc, CH_2Cl_2, RT, 2.5 h, 80%; g) HF·Pyr, CH_3CN, 0°C to RT, 1.5 h, 81%; h) Al (Hg), THF/EtOH/H_2O, RT, 82%.

Having installed the correct stereochemistry at C-3, we continued the synthetic plan to access **1** as depicted in Scheme 4. Firstly, we protected the secondary alcohol of compound **14** as the TBDMS derivative **15** (TBDMSCl, imidazole, DMAP, CH_2Cl_2, RT, 3 h, DMAP = 4-dimethylaminopyridine) in 96% yield. Next, we treated the bicyclic derivative **15** with *m*CPBA to afford the tricyclic epoxide **16** selectively, as the only diastereomer in 93% yield, after epoxidation exclusively on the upper face of the double bond of **15**. With the appropriate functionality for the natural product introduced, we undertook the key step: the generation of the decanolide structure. Thus, treatment of the tricyclic epoxide **16** with PCC in the presence of NaOAc gave rise to the highly functionalised lactone **2** in an excellent 80% yield, after an efficient oxidative cleavage–ring-expansion process. The correct structure of decanolide **2** was confirmed by X-ray analysis.[18] Finally, deprotection of the TBDMS group of **2** (HF·Pyr, CH_3CN, 0°C to RT, 81%) followed by regioselective reductive opening of the epoxide of **17** (Al (Hg), THF/EtOH/H_2O, RT, 82%) afforded **1**, with the

3*S*,4*R*,9*R* absolute configuration at the stereogenic centres, showing identical NMR spectroscopy data to those described for the natural product.[9a]

In summary, we have described a short and highly stereoselective sequence for the first enantioselective total synthesis of the naturally occurring 10-membered lactone **1**, which was obtained in only 8 steps and 12.9% overall yield starting from (*R*)-rhododendrol. Several key features of this approach are noteworthy. The starting material already possesses all of the carbon atoms present in the final target and only one protection–deprotection step is necessary. On the other hand, three selective oxidations allowed the introduction of the oxygenated functionality present in the natural product and allowed the efficient construction of the ten-membered lactone ring of the final target: an oxidative dearomatisation of the starting phenol, a hydroxy-directed epoxidation of an olefin intermediate, and a PCC-mediated oxidative cleavage–ring-expansion process of an angular hydroxy bicyclic derivative. A similar route was employed for the synthesis of the C-3 diastereoisomer of the natural product, which was obtained in only 7 steps and 15.2% overall yield. These syntheses of **1** and the C-3 epimer **10** compare favourably with the most efficient approaches to any member of the naturally occurring ten-membered lactones with similar complexity and, to the best of our knowledge, are the shortest reported to date for the construction of highly functionalised decanolides.

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Keywords: epoxidation · lactones · oxidative cleavage · oxidative dearomatization · total synthesis

[1] a) G. Rousseau, *Tetrahedron* **1995**, *51*, 2777–2849; b) L. S. Longo, Jr., F. I. Bombonato, H. M. C. Ferraz, *Quim. Nova* **2007**, *30*, 415–424; c) I. Shiina, *Chem. Rev.* **2007**, *107*, 239–273; d) H. M. C. Ferraz, F. I. Bombonato, M. K. Sano, L. S. Longo, Jr., *Quim. Nova* **2008**, *31*, 885–900.

[2] For reviews, see: a) G. Dräger, A. Kirschning, R. Thiericke, M. Zerlin, *Nat. Prod. Rep.* **1996**, *13*, 365–375; b) M. C. Ferraz, F. I. Bombonato, L. S. Longo, Jr., *Synthesis* **2007**, 3261–3285; c) V. B. Riatto, R. A. Pilli, M. M. Victor, *Tetrahedron* **2008**, *64*, 2279–2300.

[3] a) G. Illuminati, L. Mandolini, *Acc. Chem. Res.* **1981**, *14*, 95–102; b) L. Mandolini, *Adv. Phys. Org. Chem.* **1986**, *22*, 1–111; c) C. G. Kreiter, K. Lehr, M. Leyendecker, W. S. Sheldrik, R. Exner, *Chem. Ber.* **1991**, *124*, 3–12.

[4] For a general review, see: A. Parenty, X. Moreau, J.-M. Campagne, *Chem. Rev.* **2006**, *106*, 911–939.

[5] 32–45% yield; for examples, see: a) M. B. Andrus, T.-L. Shih, *J. Org. Chem.* **1996**, *61*, 8780–8785; b) P. Radha Krishna, P. V. Narasimha Reddy, *Tetrahedron Lett.* **2006**, *47*, 7473–7476; c) Y. Kobayashi, S. Yoshida, M. Asano, A. Takeuchi, H. P. Acharya, *J. Org. Chem.* **2007**, *72*, 1707–1716; d) P. Gupta, P. Kumar, *Eur. J. Org. Chem.* **2008**, 1195–1202.

[6] For recent reviews, see: a) A. Gradillas, J. Pérez-Castells, *Angew. Chem.* **2006**, *118*, 6232–6247; *Angew. Chem. Int. Ed.* **2006**, *45*, 6086–6101; b) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4564–4601; *Angew. Chem. Int. Ed.* **2005**, *44*, 4490–4527 K; c) R. H. Grubbs, *Tetrahedron* **2004**, *60*, 7117–7140; d) S. J. Connon, S. Blechert, *Angew. Chem.* **2003**, *115*, 1944–1968; *Angew. Chem. Int. Ed.* **2003**, *42*, 1900–1923; e) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140–3172; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043.

[7] D. K. Mohapatra, D. K. Ramesh, M. A. Giardello, M. S. Chorghade, M. K. Gurjar, R. H. Grubbs, *Tetrahedron Lett.* **2007**, *48*, 2621–2625, and references therein.

[8] See refs. [2b], [2c] and [5d], and the following: a) C. V. Ramana, T. P. Khaladkar, S. Chatterjee, M. K. Gurjar, *J. Org. Chem.* **2008**, *73*, 3817–3822; b) J. Liu, L. Zhang, J. He, L. He, B. Ma, X. Pana, X. She, *Tetrahedron: Asymmetry* **2008**, *19*, 906–911; c) M. Matsuda, T. Yamazaki, K.-I. Fuhshuku, T. Sugai, *Tetrahedron* **2007**, *63*, 8752–8760; d) S. Ghosh, R. V. Rao, *Tetrahedron Lett.* **2007**, *48*, 6937–6940; e) P. R. Krishna, M. Narsingam, *Synthesis* **2007**, 3627–3634.

[9] a) A. Farocq, J. Gordon, J. R. Hanson, J. A. Takahashi, *Phytochemistry* **1995**, *38*, 557–558; b) M. J. Ackland, J. R. Hanson, P. B. Hitchcock, A. H. Ratcliffe, *J. Chem. Soc. Perkin Trans. 1* **1985**, 843–847; c) V. Rukachaisirikul, S. Pramjit, Ch. Pakawatchai, M. Isaka, S. Supothina, *J. Nat. Prod.* **2004**, *67*, 1953–1955.

[10] P. R. Krishna, A. Sreeshailam, *Synlett* **2008**, 2795–2798.

[11] Y. Yuasa, S. Shibuya, Y. Yuasa, *Synth. Commun.* **2003**, *33*, 1469–1475.

[12] M. C. Carreño, M. González-López, A. Urbano, *Angew. Chem.* **2006**, *118*, 2803–2807; *Angew. Chem. Int. Ed.* **2006**, *45*, 2737–2741.

[13] S. Barradas, M. C. Carreño, M. González-López, A. Latorre, A. Urbano, *Org. Lett.* **2007**, *9*, 5019–5022.

[14] a) H. M. C. Ferraz, L. S. Longo, Jr., *J. Org. Chem.* **2007**, *72*, 2945–2950; b) H. M. C. Ferraz, L. S. Longo, Jr., *Org. Lett.* **2003**, *5*, 1337–1339.

[15] a) G. H. Posner, M. A. Hatcher, W. A. Maio, *Org. Lett.* **2005**, *7*, 4301–4303; b) M. A. Hatcher, K. Borstnik, G. H. Posner, *Tetrahedron Lett.* **2003**, *44*, 5407–5409.

[16] P. Wipf, W. Li, *J. Org. Chem.* **1999**, *64*, 4576–4577.

[17] M. Honzumi, K. Ogasawara, *Tetrahedron Lett.* **2002**, *43*, 1047–1049.

[18] CCDC-725048, 725049 and 725050 for **2**, **10** and **14**, respectively, contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[19] a) T. Ooi, K. Maruoka, *Rev. Heteroat. Chem.* **1998**, *18*, 61–85; b) K. Maruoka, Y. Araki, H. Yamamoto, *J. Am. Chem. Soc.* **1988**, *110*, 2650–2652.

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