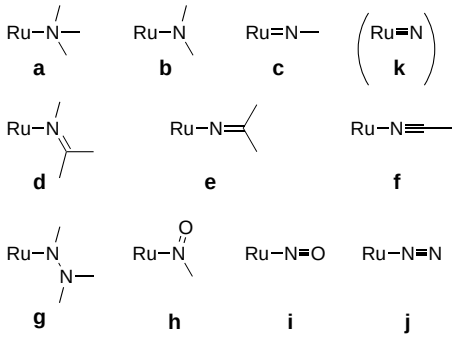
Aminations with Ru Porphyrins

Nitrido Ruthenium Porphyrins: Synthesis, Characterization, and Amination Reactions with Hydrocarbon or Silyl Enol Ethers**

Sarana Ka-Yan Leung, Jie-Sheng Huang, Jiang-Lin Liang, Chi-Ming Che, and Zhong-Yuan Zhou*

Ruthenium porphyrins constitute an unmatched family of metalloporphyrin that exhibits extraordinary versatility in binding N-donating ligands at the axial sites.[1–5] A wide variety of ruthenium porphyrins featuring axial Ru–N bonds have been prepared, including those bearing amine,[1c,3a,3b] amido,[3b–d,g] imido,[3a,c–e,g,j] imine,[3h,4] methyleneamido,[3h] nitrile,[1a,2] hydrazido,[3f] nitrosoarene,[1b,3i] nitrosyl,[5] and dinitrogen[1d] axial ligands (Scheme 1, **a**–**j**). This makes the lack of



Scheme 1. Axial Ru–N bonds in ruthenium porphyrins.

isolable ruthenium porphyrins with terminal nitrido axial ligands (Scheme 1, **k**) especially conspicuous.[6,7]

Our interest in nitrido ruthenium porphyrins stems from the particular importance of nitrido–metal (M≡N) complexes in C–N bond-formation reactions.[8] In a pioneering work by Groves and Takahashi, a nitrido manganese porphyrin, upon activation with trifluoroacetic anhydride (TFAA) to form a trifluoroacetylimido manganese (Mn=NCOCF$_3$) species, underwent NCOCF$_3$ group transfer with *cis*-cyclooctene to give an aziridine product.[8a] Subsequent works by Carreira and co-workers demonstrate that several nitrido manganese Schiff base complexes can be activated with TFAA and undergo NCOCF$_3$ group transfer with silyl enol ethers, glycols, and styrene to afford amination or aminohydroxylation products.[8b–e] Recently, Komatsu and co-workers reported asymmetric aziridination of alkenes and asymmetric amination of silyl enol ether with chiral nitrido manganese Schiff base complexes upon (*p*-MeC$_6$H$_4$SO$_2$)$_2$O or TFAA activation.[8f]

Surprisingly, all the aziridination/amination reactions of nitrido metal complexes have to date been confined to nitrido complexes of manganese, although numerous nitrido complexes of other transition metals have been reported.[9] The amination by nitrido manganese Schiff base complexes only occurred for unsaturated C–H bonds. No nitrido metalloporphyrins have been found to undergo C-H insertion reactions to afford amination products.

Herein we report the syntheses and amination reactions of nitrido ruthenium(VI) porphyrins [Ru^{VI}(por)(N)(OH)] (**1a**: por = tmp, **1b**: por = 3,4,5-MeO-tpp; see Scheme 2).[10] These nitrido ruthenium complexes were prepared by employing an unprecedented synthetic strategy for nitrido metal complexes, that is, reaction of oxo–metal complexes with an imine compound. Upon activation with TFAA, both **1a** and **1b** can aminate silyl enol ethers to give *N*-trifluoroacetylated α-amino ketones. Especially interesting is that the "**1a**/**1b** + TFAA" system can undergo C–H insertion reaction with indan to form *N*-trifluoroacetyl indan-1-ylamine. This reaction, to our knowledge, is the first amination of saturated C–H bonds of a hydrocarbon with nitrido metal complexes.

Treatment of dioxoruthenium(VI) porphyrin [Ru^{VI}(por)(O)$_2$] (por = tmp[11a] or 3,4,5-MeO-tpp[3b]) generated in situ from [Ru^{II}(por)(CO)] and excess *m*-CPBA[10] (see Scheme 2, reaction (1)) with excess HN=C*t*Bu$_2$ in dichloromethane for ≈40 min afforded a green solution, workup of which gave **1a** or **1b** as a dark purple solid in ≈85% yield (reaction (2) in Scheme 2). Both **1a** and **1b** are stable to moist air for several months in the solid state and can exist for several hours in dichloromethane solutions exposed to the atmosphere.

We found that reaction (2) shows surprisingly strong dependence on the electronic properties of the porphyrin ligand.[12] Attempts to extend reaction (2) to less electron-rich porphyrins (such as tpp[10] and ttp[10]) and electron-deficient porphyrins (such as tpfpp[10]) did not lead to formation of nitrido ruthenium porphyrins; instead, μ-oxo and nitrosyl ruthenium porphyrins were obtained, respectively.

The reaction between [Ru^{VI}(3,4,5-MeO-tpp)(O)$_2$] and HN=C*t*Bu$_2$ to form **1b** contrasts sharply with that between the same dioxo complex and HN=CPh$_2$, the latter reaction has been reported to produce bis(methyleneamido) ruthenium(IV) porphyrin [Ru^{IV}(3,4,5-MeO-tpp)(N=CPh$_2$)$_2$] in ≈65% yield under similar conditions.[3h]

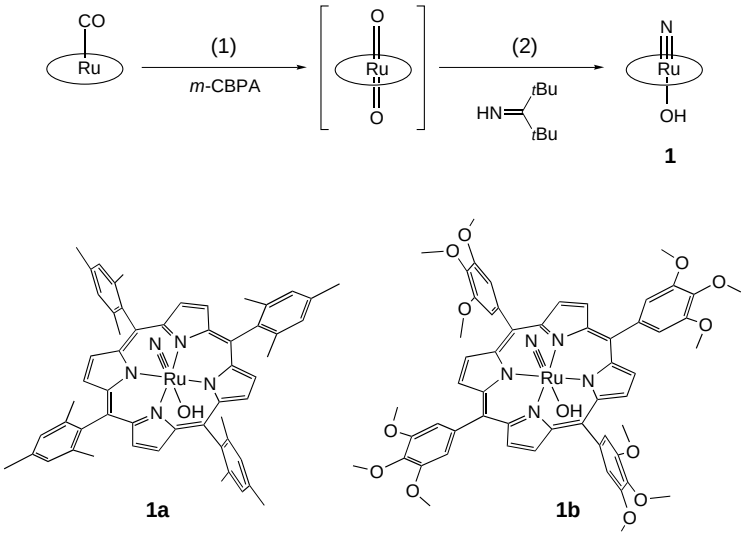
Efforts were once made to prepare **1a**/**1b** or their analogues by employing known synthetic strategies such as cleavage of the N–R bond in imido metal (M=NR) complexes and oxidation of coordinated ammines.[9b] However, these synthetic strategies did not lead to isolation of pure nitrido

[*] Prof. Dr. C.-M. Che, S. K.-Y. Leung, Dr. J.-S. Huang, J.-L. Liang
Department of Chemistry and Open Laboratory of Chemical Biology of the Institute of Molecular Technology for Drug Discovery and Synthesis
The University of Hong Kong, Pokfulam Road (Hong Kong)
Fax: (+852) 2857-1586
E-mail: cmche@hku.hk
Prof. Z.-Y. Zhou
Department of Applied Biology and Chemical Technology
The Hong Kong Polytechnic University, Hung Hom, Kowloon (Hong Kong)

[**] This work was supported by The University of Hong Kong, the Hong Kong University Foundation, the Hong Kong Research Grants Council, and the University Grants Committee of the Hong Kong SAR of China (Area of Excellence Scheme, AoE/P-10/01).

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

  0044-8249/03/11503-0354 $ 20.00+.50/0



Scheme 2. Synthesis of the nitrido ruthenium(VI) porphyrins **1**. *m*-CPBA = *meta*-chloroperoxybenzoic acid.

ruthenium porphyrins. For example, autodegradation of in situ formed bis(tosylimido) ruthenium(VI) porphyrin [Ru^{VI}(tmp)$(NTs)_2$][3d] in aerobic dichloromethane gave [Ru^{VI}(tmp)(N)(NHTs)] (**2**; reactions (3) and (4) in Scheme 3) contaminated with NH_2Ts; oxidation of the isolated bis(ammine) ruthenium(II) porphyrin [Ru^{II}(ttp)$(NH_3)_2$] (prepared from [Ru^{VI}(ttp)$(O)_2$][11b] and excess NH_3, reaction (5) in Scheme 3) with 4 equivalents of NBS[10] in dichloromethane under argon afforded [Ru^{VI}(ttp)(N)Br] (**3**; reaction (6)) contaminated by NBS.

The nitrido ruthenium(VI) porphyrins **1**–**3** are all diamagnetic and feature "oxidation-state marker" bands[3a,b] at $> 1015\ cm^{-1}$ in their IR spectra, like dioxo, oxo(imido) or bis(imido) ruthenium(VI) porphyrins.[3a,d] The following spectral features of **1**–**3** are distinctive. First, the signals of the pyrrole protons (H_β) in the ^1H NMR spectra are at $\delta = 9.00$ (**1a**), 9.09 (**2**), 9.33 (**1b**), and 9.36 ppm (**3**), which are all downfield from those of their dioxo,[3b,11] oxo(imido),[3a,g] or bis(imido)[3c,d] ruthenium(VI) counterparts. Second, the β bands in the UV/Vis spectra appear at 485–488 nm, which are substantially blue-shifted from those of other ruthenium porphyrins reported.[1–5]

In the electrospray mass spectra (ESI–MS) of **1**–**3**, intense cluster peaks corresponding to the fragments $[Ru(por)(N)]^+$ were located. The ESI–MS of **1a**, **1b**, and **3** also show prominent peaks ascribable to their parent ions. Complex **2** did not give parent-ion peaks in the ESI–MS; its axial NHTs ligand was identified on the basis of the ^1H NMR spectrum. In the IR spectra, conversion of [Ru^{II}(tmp)(CO)] into **1a** and **2** led to the appearance of a new band at $1038\ cm^{-1}$, which we tentatively assigned to the Ru≡N group.[13] Identification of the Ru≡N band for **1b** and **3** was hampered by either intense signals of the porphyrin ligand in the region of interest or impurities in the sample.

The structure of **1b** has been determined by X-ray crystallography (Figure 1),[14] and features a

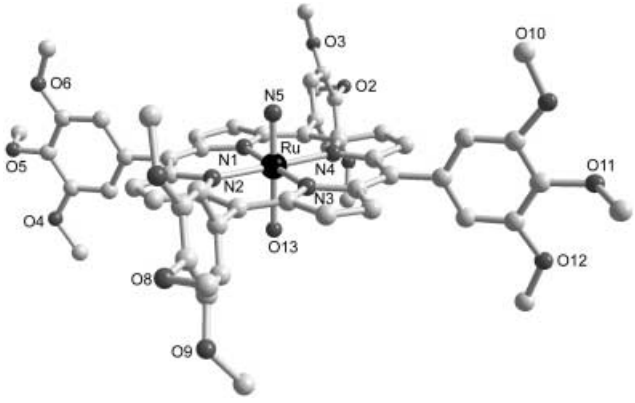
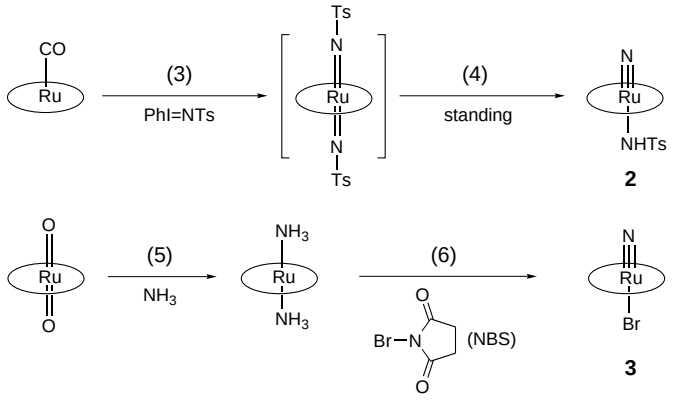


Figure 1. Molecular structure of **1b** determined by X-ray crystallography (hydrogen atoms are not shown). Selected bond lengths [Å] and bond angles [°]: Ru-N1 2.046(6), Ru-N2 2.086(6), Ru-N3 2.001(6), Ru-N4 2.026(7), Ru-N5 1.656(5), Ru-O13 2.086(7); N1-Ru-N2 92.7(2), N2-Ru-N3 88.5(2), N3-Ru-N4 88.5(3), N4-Ru-N1 90.3(3), N5-Ru-O13 177.8(3).



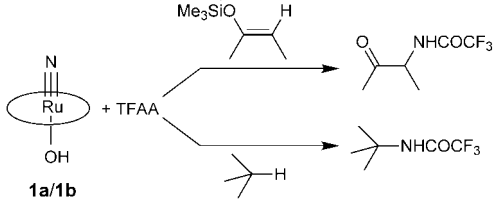
Scheme 3. Formation of the nitrido ruthenium(VI) porphyrins **2** and **3** from autodegradation of a bis(tosylimido)ruthenium(VI) porphyrin or from NBS oxidation of a bis(ammine)ruthenium(II) porphyrin.

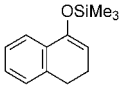
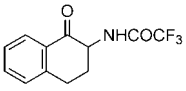
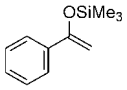
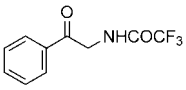
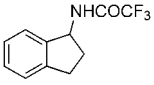
planar porphyrin ring and a Ru–N(nitrido) distance of 1.656(5) Å, slightly longer than those of nitrido ruthenium complexes with tri- or tetradentate non-porphyrin ligands (1.594–1.615 Å).[15] The Ru–O(OH) distance of 2.086(7) Å in **1b** is longer than that in [Ru(ttp)(NO)(OH)] (1.943(5) Å).[5g]

Note that the above nitrido ruthenium porphyrins can be readily converted into hexacoordinate {Ru(NO)} complexes. For example, reactions of **1b** with PhIO and MeOH in dichloromethane gave [Ru(3,4,5-MeO-tpp)(NO)(OH)] and [Ru(3,4,5-MeO-tpp)(NO)(OMe)], respectively. In an attempt to purify **3** by chromatography on an alumina column, the complex was converted into [Ru(ttp)(NO)Br] (see Supporting Information).

Interestingly, treatment of **1a** or **1b** with silyl enol ethers and TFAA in dichloromethane containing pyridine under argon for ≈5 h afforded respective *N*-trifluoroace-

Table 1: Amination reaction of **1a** or **1b** with silyl enol ethers and indan.



Entry	Substrate	Product	Yield [%]
1			68 (**1a**)
2			75 (**1b**)
3			70 (**1a**)
4			84 (**1b**)
5			52 (**1a**)
6			63 (**1b**)

tylated α-amino ketones in 68–84 % yields of isolated product (entries 1–4 in Table 1). By employing indan instead of silyl enol ethers, the same reactions gave *N*-trifluoroacetyl indan-1-ylamine in 52 (**1a**) or 63 % (**1b**) yield (determined by GC), as shown in entries 5 and 6 in Table 1. These reactions are very striking, because many non-porphyrin nitrido ruthenium complexes have been isolated, but none of these is reported to be reactive toward hydrocarbons or silyl enol ethers.[6,15,16]

The reaction of "**1a**/**1b** + TFAA" with indan to form *N*-trifluoroacetyl indan-1-ylamine is a unique approach to *N*-trifluoroacetyl amines from direct intermolecular amination of hydrocarbon saturated C–H bonds. Previous formation of *N*-substituted amines from metal-mediated stoichiometric or catalytic intermolecular amination of saturated C–H bonds of hydrocarbons was successful only for *N*-SO_2R or *N*-COPh amines.[17] We envision that the nitrido ruthenium(VI) porphyrin **1a** or **1b**, upon proper activation, might also be useful for the synthesis of other types of *N*-substituted amines by direct amination of saturated C–H bonds; such studies, together with the mechanisms of reaction (2) and the $NCOCF_3$ group-transfer reactions between "**1a**/**1b** + TFAA" and indan/silyl enol ethers, are under current investigation in our laboratory.

Received: September 10, 2002 [Z50138]

[1] a) N. Farrell, D. H. Dolphin, B. R. James, *J. Am. Chem. Soc.* **1978**, *100*, 324; b) C. Crotti, C. Sishta, A. Pacheco, B. R. James, *Inorg. Chim. Acta* **1988**, *141*, 13; c) A. J. Bailey, B. R. James, *Chem. Commun.* **1996**, 2343; d) M. J. Camenzind, B. R. James, D. Dolphin, J. W. Sparapany, J. A. Ibers, *Inorg. Chem.* **1998**, *37*, 3054.

[2] J.-T. Groves, K.-H. Ahn, R. Quinn, *J. Am. Chem. Soc.* **1988**, *110*, 4217.

[3] a) J.-S. Huang, C.-M. Che, C.-K. Poon, *J. Chem. Soc. Chem. Commun.* **1992**, 161; b) J.-S. Huang, C.-M. Che, Z.-Y. Li, C.-K. Poon, *Inorg. Chem.* **1992**, *31*, 1313; c) S.-M. Au, W.-H. Fung, M.-C. Cheng, C.-M. Che, S.-M. Peng, *Chem. Commun.* **1997**, 1655; d) S.-M. Au, J.-S. Huang, W.-Y. Yu, W.-H. Fung, C.-M. Che, *J. Am. Chem. Soc.* **1999**, *121*, 9120; e) X.-G. Zhou, X.-Q. Yu, J.-S. Huang, C.-M. Che, *Chem. Commun.* **1999**, 2377; f) X.-R. Sun, J.-S. Huang, K.-K. Cheung, C.-M. Che, *Inorg. Chem.* **2000**, *39*, 820; g) J.-S. Huang, X.-R. Sun, S. K.-Y. Leung, K.-K. Cheung, C.-M. Che, *Chem. Eur. J.* **2000**, *6*, 334; h) J.-S. Huang, S. K.-Y. Leung, K.-K. Cheung, C.-M. Che, *Chem. Eur. J.* **2000**, *6*, 2971; i) J.-L. Liang, J.-S. Huang, Z.-Y. Zhou, K.-K. Cheung, C.-M. Che, *Chem. Eur. J.* **2001**, *7*, 2306; j) J.-L. Liang, J.-S. Huang, X.-Q. Yu, N. Zhu, C.-M. Che, *Chem. Eur. J.* **2002**, *8*, 1563.

[4] a) C. Morice, P. Le Maux, G. Simonneaux, *Tetrahedron Lett.* **1996**, *37*, 6701; b) C. Morice, P. Le Maux, C. Moinet, G. Simonneaux, *Inorg. Chim. Acta* **1998**, *273*, 142.

[5] a) A. Antipas, J. W. Buchler, M. Gouterman, P. D. Smith, *J. Am. Chem. Soc.* **1978**, *100*, 3015; b) K. M. Kadish, V. A. Adamian, E. V. Caemelbecke, Z. Tan, P. Tagliatesta, P. Bianco, T. Boschi, G.-B. Yi, M. A. Khan, G. B. Richter-Addo, *Inorg. Chem.* **1996**, *35*, 1343; c) D. S. Bohle, P. A. Goodson, B. D. Smith, *Polyhedron* **1996**, *15*, 3147; d) S. J. Hodge, L.-S. Wang, M. A. Khan, V. G. Young, Jr., G. B. Richter-Addo, *Chem. Commun.* **1996**, 2283; e) K. M. Miranda, X. Bu, I. Lorkovic, P. C. Ford, *Inorg. Chem.* **1997**, *36*, 4838; f) G.-B. Yi, M. A. Khan, D. R. Powell, G. B. Richter-Addo, *Inorg. Chem.* **1998**, *37*, 208; g) D. S. Bohle, C.-H. Hung, B. D. Smith, *Inorg. Chem.* **1998**, *37*, 5798; h) I. M. Lorkovic, K. M. Miranda, B. Lee, S. Bernhard, J. R. Schoonover, P. C. Ford, *J. Am. Chem. Soc.* **1998**, *120*, 11674; i) J. Lee, G.-B. Yi, M. A. Khan, G. B. Richter-Addo, *Inorg. Chem.* **1999**, *38*, 4578; j) G. B. Richter-Addo, R. A. Wheeler, C. A. Hixson, L. Chen, M. A. Khan, M. K. Ellison, C. E. Schulz, W. R. Scheidt, *J. Am. Chem. Soc.* **2001**, *123*, 6314.

[6] L. Bonomo, E. Solari, R. Scopelliti, C. Floriani, *Angew. Chem.* **2001**, *113*, 2597; *Angew. Chem. Int. Ed.* **2001**, *40*, 2529.

[7] Ruthenium porphyrins bearing a bridging nitrido ligand have been isolated, see: W.-H. Leung, J. L. C. Chim, W. Lai, L. Lam, W.-T. Wong, W. H. Chan, C.-H. Yeung, *Inorg. Chim. Acta* **1999**, *290*, 28. We noticed that in a previous synthesis of a terminal nitrido complex of ruthenium(VI) porphyrin, [Ru^{VI}(4-Cl-tpp)(N)(OH)] (H_2(4-Cl-tpp) = *meso*-tetrakis(4-chlorophenyl)-porphyrin), from a biphasic (CH_2Cl_2/H_2O) reaction of in situ formed [Ru^{VI}(4-Cl-tpp)$(O)_2$] with $NH_3 \cdot H_2O$ (see: Z.-Y. Li, C.-M. Che, C.-K. Poon, *Wuhan Univ. J. Nat. Sci.* **1996**, *1*, 89), the "nitrido" species (which was not structurally characterized) should be reformulated as a hexacoordinate {Ru(NO)} complex, [Ru(4-Cl-tpp)(NO)(X)], according to its UV/Vis spectral data (Soret band: 412 nm, β band: 558 nm).

[8] Selected examples: a) J. T. Groves, T. Takahashi, *J. Am. Chem. Soc.* **1983**, *105*, 2073; b) J. Du Bois, J. Hong, E. M. Carreira, M. W. Day, *J. Am. Chem. Soc.* **1996**, *118*, 915; c) J. Du Bois, C. S. Tomooka, J. Hong, E. M. Carreira, *J. Am. Chem. Soc.* **1997**, *119*, 3179; d) J. Du Bois, C. S. Tomooka, J. Hong, E. M. Carreira, *Acc. Chem. Res.* **1997**, *30*, 364; e) J. Du Bois, C. S. Tomooka, J. Hong, E. M. Carreira, M. W. Day, *Angew. Chem.* **1997**, *109*, 1722; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1645; f) S. Minakata, T. Ando, M. Nishimura, I. Ryu, M. Komatsu, *Angew. Chem.* **1998**, *110*, 3596; *Angew. Chem. Int. Ed.* **1998**, *37*, 3392.

[9] a) W. A. Nugent, J. M. Mayer, *Metal-Ligand Multiple Bonds*, Wiley, New York, **1988**; b) K. Dehnicke, J. Strähle, *Angew. Chem.* **1992**, *104*, 978; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 955.

  0044-8249/03/11503-0356 $ 20.00+.50/0

[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≡N formation from reaction (2).
[13] The frequency of this new band is comparable to the Ru≡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).
[15] P. M. Chan, W.-Y. Yu, C.-M. Che, K.-K. Cheung, *J. Chem. Soc. Dalton Trans.* **1998**, 3183.
[16] We treated $[NnBu_4][Ru^{VI}(N)Cl_4]$ (prepared as described in W. P. Griffith, D. Pawson, *J. Chem. Soc. Dalton Trans.* **1973**, 1315) and $[Ru^{VI}(N)(L)Cl]$ (H_2L = 2,6-bis(2-hydroxy-2,2-diphenylethyl)-pyridine, prepared as described in ref. [15]) with TFAA and the silyl enol ethers shown in Table 1 under the conditions similar to those for **1a**/**1b** but obtained no amination products from the reaction mixtures.
[17] Selected examples: a) R. Breslow, S. H. Gellman, *J. Chem. Soc. Chem. Commun.* **1982**, 1400; b) J. P. Mahy, G. Bedi, P. Battioni, D. Mansuy, *Tetrahedron Lett.* **1988**, *29*, 1927; c) I. Nägeli, C. Baud, G. Bernardinelli, Y. Jacquier, M. Moran, P. Müller, *Helv. Chim. Acta* **1997**, *80*, 1087; d) S.-M. Au, J.-S. Huang, C.-M. Che, W.-Y. Yu, *J. Org. Chem.* **2000**, *65*, 7858, and references therein; e) Y. Kohmura, T. Katsuki, *Tetrahedron Lett.* **2001**, *42*, 3339.

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 $\mu g\,mL^{-1}$ 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

[*] Prof. I. Paterson, M. Tudge
University Chemical Laboratory
Lensfield Road, Cambridge, CB2 1EW (UK)
Fax: (+44) 1223-336-362
E-mail: ip100@cus.cam.ac.uk

[**] We thank the EPSRC (studentship to M.T. and GR/N08520), the EU (Network HPRN-CT-2000-00018), and Merck, Pfizer, and Novartis for support.

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