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[10] *Trans*-lycopene was obtained as a major product (80 % or more) with a small amount (20 % or less) of *cis*-lycopene. This latter product was believed to be the 9-*cis* isomer on the basis of characteristic peaks at $\delta = 6.06$ and 6.79 in the ^{1}H NMR spectrum.[3c] Base-promoted elimination of the sulfonyl groups produced mostly *trans* double bonds.

Dehydrogenation of $[\{(silox)_3Nb\}_2(\eta\text{-}1,2;\eta\text{-}5,6\text{-}C_8H_8)]$ (silox = *t*Bu_3SiO) to $[\{(silox)_3Nb\}_2(\eta\text{-}1,2;\eta\text{-}5,6\text{-}C_8H_6)]$ and Its Subsequent Alkene-to-Alkylidene Rearrangement**

Adam S. Veige, Peter T. Wolczanski,* and Emil B. Lobkovsky

The observed pyridine ring-opening of $[(silox)_3Nb(\eta\text{-}C,N\text{-}C_5H_5N)]$ (silox = *t*Bu_3SiO) to $[(silox)_3Nb{=}CHCH{=}CHCH{=}CHN{=}Nb(silox)_3]$, and related picoline chemistry[1, 2] suggested that carbon – carbon bond scission might occur by similar pathways. 1,3,5,7-Cyclooctatetraene (COT) was considered a prime candidate for ring opening because of its lack of resonance stabilization energy, but in binding to two $[(silox)_3Nb]$ units, COT functions as an aromatic dianion, which directs the chemistry toward C–H bond activation, dehydrogenation, and a subsequent alkene-to-alkylidene rearrangement.

Reduction of $[(silox)_3NbCl_2]$ (**1**)[3] with Na/Hg in THF with three equivalents of COT present resulted in the isolation of brown $[(silox)_3Nb(\eta\text{-}C_8H_8)]$ (**2**-COT, 40 %) [Eq. (1)].

$$[(silox)_3NbCl_2] + L\ (\text{excess}) \xrightarrow[Na/Hg,\ -2\,NaCl]{THF,\ 24\,h} [(silox)_3NbL] \qquad (1)$$
$$\mathbf{2}\text{-L}\ (L = COT,\ cC_6H_{10})$$

Abstraction of 4-picoline from $[(silox)_3Nb(\eta\text{-}C,N\text{-}4\text{-}MeC_5H_4N)]$ (**2**-4-pic) by $[(silox)_3Ta]$[2] in the presence of **2**-COT afforded $[(silox)_3Ta(\eta\text{-}4\text{-pic})]$ and burgundy, crystalline $[\{(silox)_3Nb\}_2(\eta\text{-}1,2;\eta\text{-}5,6\text{-}C_8H_8)]$ ($\mathbf{2}_2$-COT, 33 %, Scheme 1). The synthesis of $\mathbf{2}_2$-COT must occur under mild conditions to avoid further reaction (vide infra). An X-ray crystal structure determination of $\mathbf{2}_2$-COT[4, 5] revealed the $[(silox)_3Nb]$ moieties (d(Nb–C) = 2.20(5) Å (av))[6, 7] in an *anti*-η^2,η^2-configuration about a planar COT ligand, although disorder problems hampered further analysis. The insolubility of $\mathbf{2}_2$-COT in unreactive hydrocarbon solvents prevented spectral characterization.

Upon thermolysis of two equivalents of $[(silox)_3Nb(\eta\text{-}C,N\text{-}4\text{-}MeC_5H_4N)]$ (**2**-4-pic) and COT, **2**-COT and presumably $\mathbf{2}_2$-COT were generated in situ, and dehydrogenation led to the gold-brown cyclooctatrieneyne[8] complex, $[\{(silox)_3Nb\}_2(\eta\text{-}1,2;\eta\text{-}5,6\text{-}C_8H_6)]$ (**4**; Scheme 1). Although **4** was isolated in 50 % yield, ^{1}H NMR spectroscopy revealed the conversion to be > 95 % when the reaction was monitored in a sealed tube (C_6D_6). Olefin substitution reactions of **2**-4-pic, such as the synthesis of the 1-butene complex, $[(silox)_3Nb(\eta^2\text{-}C_4H_8)]$ (**2**-

[*] Prof. P. T. Wolczanski, A. S. Veige, E. B. Lobkovsky
Department of Chemistry & Chemical Biology
Baker Laboratory, Cornell University
Ithaca, New York 14853 (USA)
Fax: (+1) 607-255-4137
E-mail: ptw2@cornell.edu

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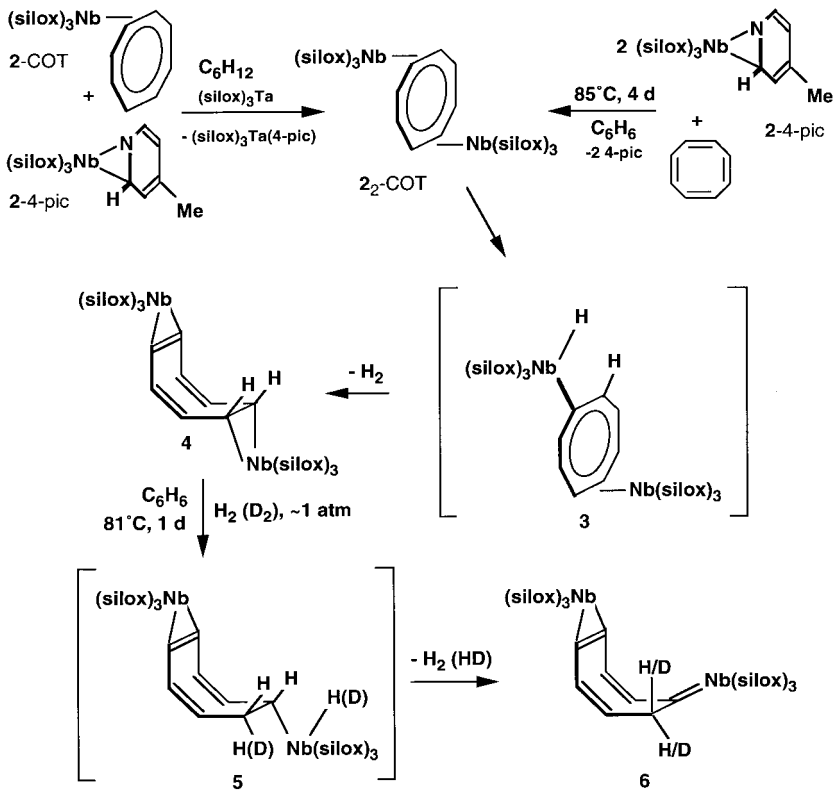

Scheme 1. Synthesis of $\mathbf{2}_2$-COT and its subsequent reactions to give **6**.

C_4H_8) [Eq. (2)], had been previously established,[2] and provided a practical synthesis of **4**.

$$[(silox)_3Nb(4\text{-pic})] + 1\text{-butene} \xrightarrow[C_6H_6]{85\,^\circ C,\ 13\,h} [(silox)_3Nb(\eta^2\text{-}C_4H_8)] + 4\text{-picoline} \quad (2)$$

2-4-pic — **2**-C_4H_8

Direct thermolysis of $\mathbf{2}_2$-COT also afforded **4**, but in lesser purity. The single-crystal X-ray structure determination of **4** is shown in Figure 1.[5, 9] 1,2-Alkyne ligation (d(Nb–C) = 2.091(8), 2.092(9) Å; d(C–C) = 1.364(14) Å) is distinct from 5,6-alkene binding (d(Nb–C) = 2.153(10), 2.177(9) Å; d(C–C) = 1.335(12) Å) as the near planarity of the C8-C1-Nb-C2-C3 atoms attests.

The reversibility of the $\mathbf{2}_2$-COT → **4** conversion was probed by thermolysis of **4** under H_2. Instead, dihydrogen catalyzed the rearrangement of **4** to the orange alkylidene–yne complex, [{(silox)$_3$Nb}$_2$(η^1;η^2-4,5-C_8H_6)] (**6**, Scheme 1). Although **6** was isolated in about 40% yield, the reaction was observed to be virtually quantitative when monitored in a sealed tube by ^{1}H NMR spectroscopy; without dihydrogen, the conversion took three days at 155 °C. The single-crystal X-ray structure determination of **6** is shown in Figure 2.[5, 10] The alkyne is slightly skewed (d(Nb–C) = 2.056(10), 2.145(11) Å), the niobium–alkylidene bond length of 1.971(10) Å is normal,[1, 11] and the methylene is a substituent on the alkylidene moiety.

When [{(silox)$_3$Nb}$_2$(η^1;η^2-4,5-C_8H_5D)] (**6**-D) was synthesized from **4** and D_2 in a sealed tube, its ^{1}H NMR spectrum revealed that the intensity of the methylene resonance at δ = 4.70 was halved, consistent with the incorporation of one deuterium atom. The overlapping doublet of triplets at δ = 6.31 assigned to a proton adjacent to the methylene group became a doublet of doublets, and HD (solution) was observed as a 1:1:1 triplet at δ = 4.42 (C_6D_6). Variable-temperature ^{1}H NMR resonance experiments provided evidence in solution for the ring pucker observed in the solid-state structure of **6**. Decoalescence of the CHH′ group into two broad resonances was attributed to a ring inversion barrier of $\Delta G^{\ddagger}$ = 10.7(3) kcal mol^{-1}. The labeling experiment is consistent with hydrogenation of the alkene of **4** to form transient alkyl-hydride **5**, followed by an α-H-abstraction[12] by the hydride to give the alkylidene **6** (see Scheme 1,). The hydrogenation of **4** may occur through a

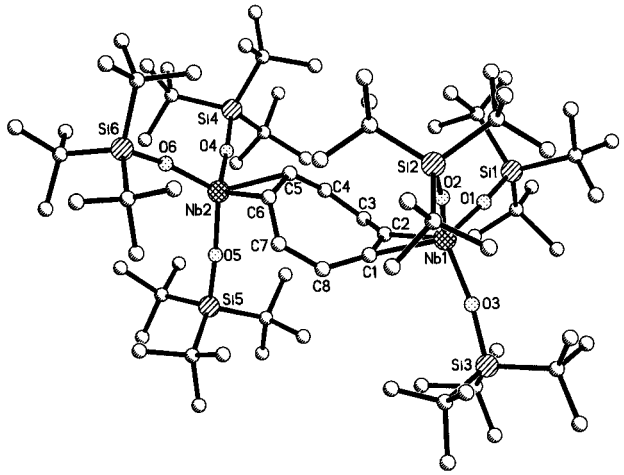

Figure 1. Molecular structure of **4**. Selected distances [Å] and angles [°]: Nb1-O 1.903(31) av, Nb2-O 1.912(47) av; Nb1-C1-C8 150.9(7), Nb1-C2-C3 152.3(8), Nb1-C1-C2 71.4(5), Nb1-C2-C1 71.4(5), C2-C1-C8 136.7(9), C1-C2-C3 135.7(9), Nb2-C5-C4 111.2(6), Nb2-C6-C7 124.3, Nb2-C5-C6 72.6(6), Nb2-C6-C5 70.7(6), C4-C5-C6 131.3(9), C5-C6-C7 135.8(9).

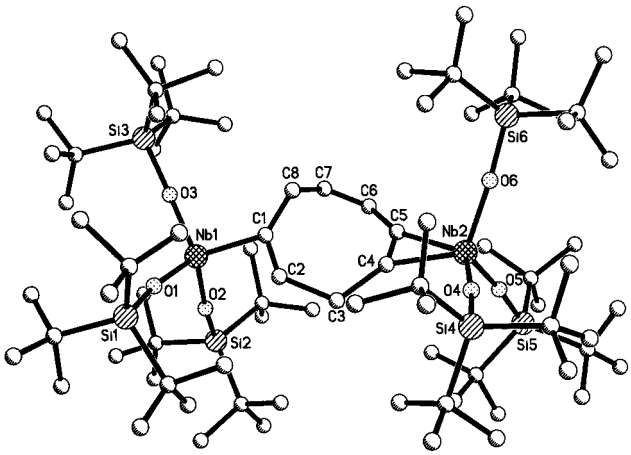

Figure 2. Molecular structure of **6**; C8 is the the methylene group. Selected distances [Å] and angles [°]: Nb1-O 1.897(23) av, Nb2-O 1.900(30) av; Nb1-C1-C2 107.0(8), Nb1-C1-C8 129.2(8), C1-C8-C7 108.5(9), Nb2-C4-C3 149.4(8), Nb2-C5-C6 156.8(8), Nb2-C4-C5 77.5(7), Nb2-C5-C4 69.3(7), C3-C4-C5 129.0(10), C4-C5-C6 132.2(11).

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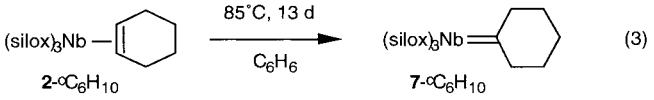
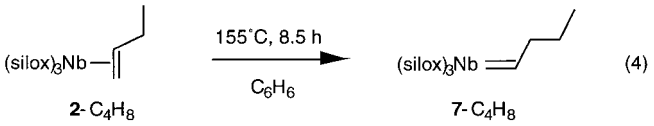
standard H_2 (D_2) oxidative addition to the putative Nb^{III}–alkene center of **4** followed by insertion to give **5**, or by a mechanistically indistiguishable σ-bond metathesis path.

The COT dehydrogenation and rearrangement reactions prompted an investigation of simple olefin complexes. Extended thermolysis of $[(silox)_3Nb(\eta^2\text{-}cC_6H_{10})]$ (**2**-cC_6H_{10}, [Eq. (1)], 40%) induced the rearrangement to the cyclohexylidene complex, $[(silox)_3Nb{=}\overline{C(CH_2)_4CH_2}]$ (**7**-cC_6H_{10}, 69% yield) [Eq. (3)]. Likewise, rearrangement of 1-butene



(3)

complex $[(silox)_3Nb(\eta^2\text{-}C_4H_8)]$ (**2**-C_4H_8) to the butylidene complex $[(silox)_3Nb{=}CH(CH_2)_2CH_3]$ (**7**-C_4H_8) was evidenced [Eq. (4)]. Thermolyses under H_2 led to olefin hydrogenation.



(4)

As Scheme 1 indicates, a logical dehydrogenation sequence involves C–H bond activation of **2**$_2$-COT to give an intermediate alkenyl–hydride (**3**), followed by a β-H abstraction by the hydride[13–15] to afford **4** and dihydrogen. An alternative path requires β-H elimination to a d^0 alkyne–dihydride intermediate and subsequent elimination of H_2. Upon C–H bond activation, the COT likely remains a planar dianion in the alkenyl hydride (**3**) derived from **2**$_2$-COT. A β-abstraction by the niobium hydride of **3** is aided by the favorable geometry of the planar COT, whose β-hydrogen atom is jammed into the Nb center ($\sphericalangle$Nb-C-C $\sim \sphericalangle$/C-C-H $\sim 112.5^\circ$); β-abstractions are known to be exquisitely sensitive to geometry.[13] An alkene-to-alkylidene transformation[16–20] would incur a disruption in the resonance stabilization energy of the $C_8H_8^{2-}$ ligand of **2**$_2$-COT. As Figure 1 reveals, the dehydro-COT ligand of **4** has lost its dianionic character, hence its rearrangement to the alkylidene occurs rather than another dehydrogenation. Investigations continue into the mechanism of the olefin-to-alkylidene (e.g., **4** →**6**, **2**-C_4H_8 → **6**-C_4H_8 and **2**-cC_6H_{10} →**6**-cC_6H_{10}) rearrangements that provide a rationale for the generation of olefin metathesis catalysts.

Experimental Section

All manipulations were performed by using either glovebox (N_2) or high-vacuum techniques (Ar), and dried, deoxygenated solvents.

2-COT: A 50 mL flask was charged with $[(silox)_3NbCl_2]$ (**1**) (1.00 g, 1.23 mmol), 1,3,5,7-cyclooctatetraene (386 mg, 3.70 mmol), 0.9% Na/Hg (2.1 equiv, 70 mg Na in 7.75 g Hg) and THF (20 mL) at 77 K. Upon stirring at 23 °C for 28 h, dark brown **2**-COT (410 mg, 40%) was obtained from cold (−78 °C) diethyl ether. ^{1}H NMR (C_6D_6, 23 °C, TMS): $\delta = 1.23$ (s, 81 H; *t*Bu), 5.64 (s, 8H; C_8H_8); $^{13}C\{^1H\}$ NMR: $\delta = 24.18$ ($C(CH_3)_3$), 31.35 ($C(CH_3)_3$), 112.17 (HC); elemental analysis calcd (%) for $C_{44}H_{89}Si_3O_3Nb$: C 62.7, H 10.6; found: C 60.4, H 10.1.

2-cC_6H_{10}: A 100 mL flask charged with **1** (1.50 g, 1.85 mmol), 0.65% Na/Hg (2.1 equiv, 89 mg Na in 13.76 g Hg), C_6H_{10} (3 mL), and THF (30 mL, 77 K). Upon stirring at 23 °C for 12 h, green **2**-cC_6H_{10} (600 mg, 40%) was obtained from hexanes. ^{1}H NMR (400 MHz, C_6D_6, 23 °C, TMS): $\delta = 1.25$ (s, 81 H; *t*Bu), 1.50–1.86 (m, 4H; $C_\gamma H_2$), 2.38–2.66 (m, 4H; $C_\beta H_2$), 2.78 (m, 2H; $C_\alpha H$); $^{13}C\{^1H\}$ NMR (C_6D_6, 23 °C): $\delta = 23.90$ ($C(CH_3)_3$), 25.07 (C_γ), 28.46 (C_β), 31.21 ($C(CH_3)_3$), 70.76 (C_α); elemental analysis calcd (%) for $C_{42}H_{91}Si_3O_3Nb$: C 61.4, H 11.2; found: C 61.2, H 11.0.

2$_2$-COT: A 25 mL vial was charged with a mixture of [(silox)$_3$Nb(4-pic)] (**2**-4-pic) (209 mg, 0.252 mmol) and [(silox)$_3$Ta] (208 mg, 0.252 mmol). The mixture was dissolved in C_6H_{12} (5 mL), shaken vigorously for 2 min, and left undisturbed for 45 min; a solution of **2**-COT (230 mg, 0.252 mmol) in cyclohexane (3 mL) was added. The solution turned dark burgundy after it had been shaken vigorously for 30 s. Burgundy **2**$_2$-COT precipitated (260 mg, 33%) from this solution after it had been left to stand undisturbed for 24 h.

4: A 25 mL flask charged with **2**-4-pic (500 mg, 0.600 mmol), 1,3,5,7-cyclooctatetraene (0.5 equiv, 31 mg, 0.30 mmol), and benzene (20 mL) was refluxed at 85 °C for four days. Golden brown **4** was isolated from pentane (232 mg, 50%). ^{1}H NMR (C_6D_6, 23 °C, TMS): $\delta = 1.25$ (s, 81 H; *t*Bu), 1.33 (s, 81 H; *t*Bu), 3.19 (s, 2H, Nb(η^2-CHCH)), 6.81 (m, 2H; −CH=), 6.98 (m, 2H; −CH=); $^{13}C\{^1H\}$ NMR: $\delta = 23.94$ ($C(CH_3)_3$), 24.18 ($C(CH_3)_3$), 31.39 ($C(CH_3)_3$) 31.43 ($C(CH_3)_3$), 80.16 (Nb(η^2-CHCH)), 125.42, 129.07 (CH=CH).

2-C_4H_8: A 50 mL bomb flask was charged with **2**-4-pic (500 mg, 0.600 mmol), C_6H_6 (20 mL), and 1-butene (ca. 5 equiv) at 77 K and placed in an 85 °C oil bath for 13 h. Green **2**-C_4H_8 (385 mg, 81%) was isolated upon removal of the volatiles. ^{1}H NMR (C_6D_6, 23 °C, TMS): $\delta = 1.24$ (s, 81 H; *t*Bu), 1.35 (t, 3H; CH_3), 1.73 (m, 1H; CH_2=CH−), 1.95 (dd, 1H; CH_2=CH), 2.5 (m, 1H; CH_2=CH), 2.69 (m, 2H; CH_2); $^{13}C\{^1H\}$: $\delta = 21.14$ (CH_3), 23.85 ($C(CH_3)_3$), 31.11 ($C(CH_3)_3$) 33.82 (CH_2), 70.12, 84.02 (CH_2=CH); elemental analysis calcd (%) for $C_{40}H_{89}Si_3O_3Nb$: C 60.4, H 11.3; found: C 60.3, H 11.3.

6: A 50 mL bomb charged with **4** (80 mg, 0.050 mmol), benzene (10 mL) and H_2 (500 Torr; 77 K) was placed in a 70 °C oil bath for about two days. Crystallization from pentane at −78 °C afforded orange **6** (30 mg, 40%). ^{1}H NMR (C_6D_6, 23 °C, TMS): $\delta = 1.27$ (s, 81 H; *t*Bu), 1.32 (s, 81 H; *t*Bu), 4.70 (br d, $^3J = 8$ Hz, 2H; CH_2), 6.31 (dt, $^3J = 10$, 8 Hz, 1H; CH_2CH=), 7.20 (d, $^3J = 10$ Hz, 1H; =CH−), 8.30 (d, $^3J = 11$ Hz, 1H; Nb=C*CH*=CH−), 5.70 (d, $^3J = 11$ Hz, 1H; =CH−); $^{13}C\{^1H\}$ NMR (C_6D_6, 23 °C): $\delta = 23.36$ ($C(CH_3)_3$), 23.45 ($C(CH_3)_3$), 30.68 ($C(CH_3)_3$) 30.90 ($C(CH_3)_3$), 41.82 (CH_2), 111.75, 132.34, 134.73, 137.43 (−C=), 206.63, 211.54 (NbCC).

7-cC_6H_{10}: A 50 mL glass bomb charged with **2**-cC_6H_{10} (600 mg, 0.732 mmol) and benzene (25 mL) was placed in an 85 °C bath for 13 days. Green **7**-cC_6H_{10} (415 mg, 69%) was obtained from pentane. ^{1}H NMR (C_6D_6, 23 °C, TMS): $\delta = 1.16$ (m, 2H; $C_\delta H_2$), 1.28 (s, 81 H; *t*Bu), 1.59 (m, 4H; $C_\gamma H_2$), 3.78 (m, 4H; $C_\beta H_2$); $^{13}C\{^1H\}$ NMR: $\delta = 23.67$ ($C(CH_3)_3$), 26.96 (C_δ), 29.12 (C_γ), 31.07 ($C(CH_3)_3$), 40.99 (C_β), C_α not observed; elemental analysis calcd (%) for $C_{42}H_{89}Si_3O_3Nb$: C 61.6, H 11.9; found: C 60.9, H 11.8.

7-C_4H_8: A 50 mL bomb charged with **2**-C_4H_8 (350 mg, 0.440 mmol) and benzene (20 mL) was heated at 155 °C for 8.5 h. Red **7**-C_4H_8 (90 mg, 26%) was obtained from cold (−78 °C) Et_2O. ^{1}H NMR (C_6D_6, 23 °C, TMS): $\delta =$ 0.86 (t, $J = 7.2$ Hz, 3H; CH_3), 1.12 (m, 2H; CH_2), 1.29 (s, 81 H; *t*Bu), 3.49 (m, $J = 7.2$ Hz, 2H; CH_2), 8.17 (bs, 1H; Nb=CH); $^{13}C\{^1H\}$ NMR: $\delta = 13.74$ (CH_3), 26.71 (CH_2), 23.96 ($C(CH_3)_3$), 30.99 ($C(CH_3)_3$), 44.10 (CH_2), 249.0 (Nb=C, HMQC).; elemental analysis calcd (%) for $C_{40}H_{89}Si_3O_3Nb$: C 60.4, H 11.3; found: C 60.2, H 11.4.

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[4] **2**$_2$-COT: triclinic; $P\bar{1}$; $a = 12.297(3)$, $b = 12.424\,3)$, $c = 17.864(4)$ Å, $\alpha =$ 79.61(3), $\beta = 83.19(3)$, $\gamma = 78.57(3)^\circ$; $V = 2621.5(9)$ Å^3; $Z = 2$, $H_{97}C_{46}O_3Si_3Nb$; $T = 173(2)$ K; $\lambda = 0.71073$; 9126 reflections, 5396

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independent; $R1 = 0.0793$ ($I > 2\sigma(I)$), $wR2 = 0.1523$; $\mu = 0.332\ mm^{-1}$ (SADABS); full-matrix, least-squares on F^2.

[5] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-163099 (**2**$_2$-COT), CCDC-163100 (**4**), and CCDC-163101 (**6**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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[9] **4**: triclinic; $P\bar{1}$; $a = 13.0793(5)$, $b = 13.1076(4)$, $c = 31.0368(11)$ Å, $\alpha = 86.89(1)$, $\beta = 89.21(1)$, $\gamma = 60.82(1)^\circ$; $V = 4638.2\ 3)$ Å^3; $Z = 2$, $H_{165}C_{80}O_6Si_6Nb_2$; $T = 173(2)$ K; $\lambda = 0.71073$; 20040 reflections, 12883 independent; $R1 = 0.0805$ ($I > 2\sigma(I)$), $wR2 = 0.1759$; $\mu = 0.368\ mm^{-1}$ (SADABS); full matrix, least squares on F^2.[5]

[10] $\mathbf{6}\cdot C_6H_6$: monoclinic, $P2_1/c$; $a = 24.6813(4)$, $b = 17.6046(3)$, $c = 25.4832(4)$ Å, $\beta = 116.96(1)^\circ$; $V = 9869.5(3)$ Å^3; $Z = 4$, $H_{171}C_{86}O_6Si_6Nb_2$; $T = 173(2)$ K; $\lambda = 0.71073$; 56059 reflections, 21816 independent; $R1 = 0.0864$ ($I > 2\sigma(I)$, 14073 reflections), $wR2 = 0.2119$; $\mu = 0.368\ mm^{-1}$ (SADABS); full-matrix, least-squares on F^2.[5]

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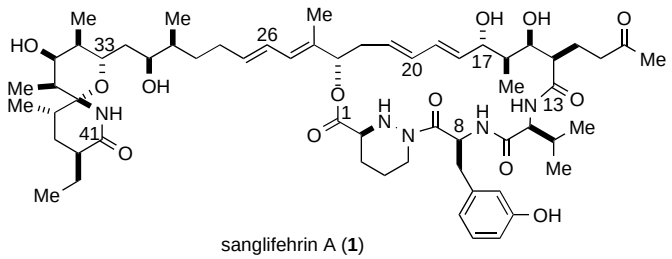
Enantioselective Total Synthesis of the Cyclophilin-Binding Immunosuppressive Agent Sanglifehrin A**

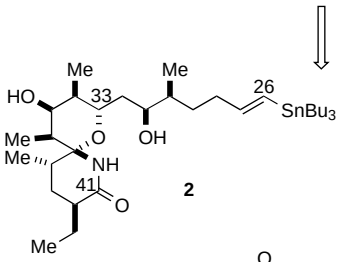
Maosheng Duan and Leo A. Paquette*

The sanglifehrins are structurally unusual Streptomyces metabolites discovered in a soil sample from Malawi.[1] The A factor **1** holds particular interest because of its strong cyclophilin-binding properties and remarkable capability to inhibit the proliferation of B and T cells. Since neither FK binding protein binding activity nor calcineurin-inhibiting capability is displayed, **1** exerts its powerful immunosupressive action in a manner quite different from that adopted by cyclosporin A, FK506, and rapamycin.[2, 3] The complex structural and stereochemical features associated with **1** and its congeners, ultimately corroborated by partial[4] and total synthesis,[5] have provided a bevy of challenging opportunities for de novo molecular assembly.

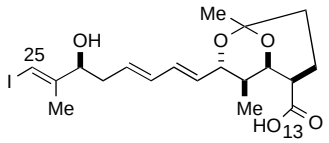
Recent synthetic efforts in this laboratory have resulted in the successful acquisition of certain subunits central to the construction of sanglifehrin A (**1**) in convergent and highly enantiocontrolled fashion.[6] Herein, we report useful refinements in these protocols as well as the successful conjoining of components **2** – **4** to arrive at **1** having all of its seventeen stereogenic centers properly installed.



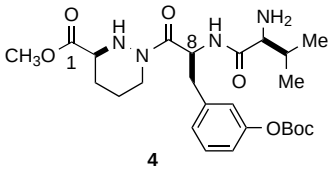
sanglifehrin A (**1**)



2



3



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[*] Prof. Dr. L. A. Paquette, M. Duan
Evans Chemical Laboratories
The Ohio State University
100 West 18th Avenue, Columbus, OH 43210 (USA)
Fax: (+1) 614-292-1685
E-mail: paquette.1@osu.edu

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