

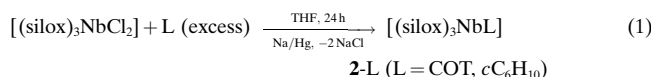
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- [10] *Trans*-lycopene was obtained as a major product (80 % or more) with a small amount (20 % or less) of *cis*-lycopene. This latter product was believed to be the 9-*cis* isomer on the basis of characteristic peaks at $\delta = 6.06$ and 6.79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

Dehydrogenation of $[(\text{silox})_3\text{Nb}]_2(\eta\text{-}1,2;\eta\text{-}5,6\text{-C}_8\text{H}_8)$ ($\text{silox} = t\text{Bu}_3\text{SiO}$) to $[(\text{silox})_3\text{Nb}]_2(\eta\text{-}1,2;\eta\text{-}5,6\text{-C}_8\text{H}_6)$ and Its Subsequent Alkene-to-Alkylidene Rearrangement**

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

The observed pyridine ring-opening of $[(\text{silox})_3\text{Nb}(\eta\text{-C}_5\text{H}_5\text{N})]$ ($\text{silox} = t\text{Bu}_3\text{SiO}$) to $[(\text{silox})_3\text{Nb}=\text{CHCH}=\text{CHCH}=\text{CHN}=\text{Nb}(\text{silox})_3]$, 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 $[(\text{silox})_3\text{Nb}]$ 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 $[(\text{silox})_3\text{NbCl}_2]$ (**1**)^[3] with Na/Hg in THF with three equivalents of COT present resulted in the isolation of brown $[(\text{silox})_3\text{Nb}(\eta\text{-C}_8\text{H}_8)]$ (**2**-COT, 40 %) [Eq. (1)].

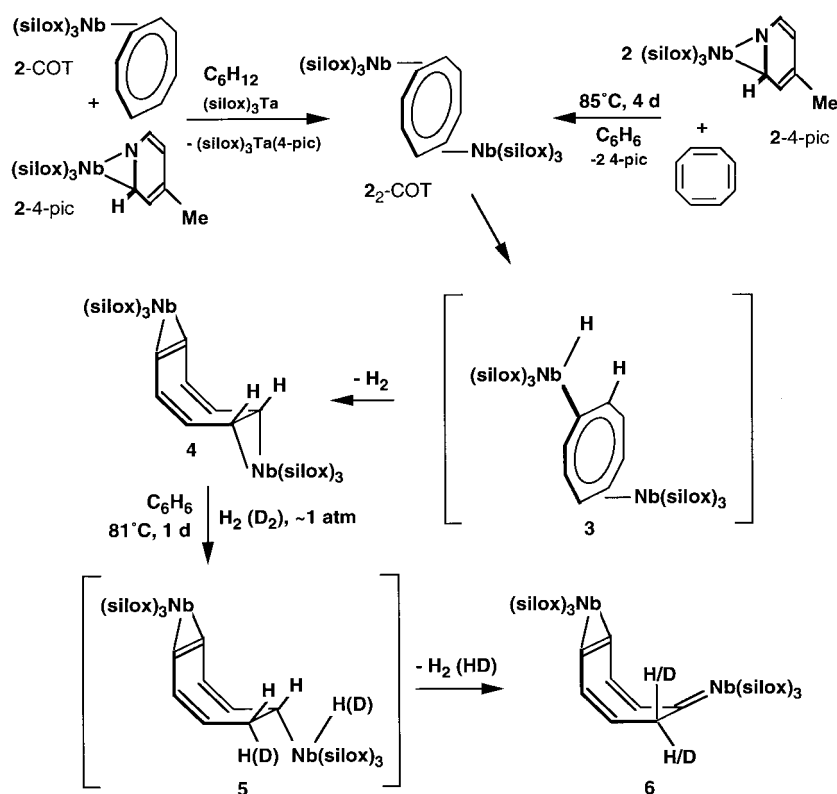


Abstraction of 4-picoline from $[(\text{silox})_3\text{Nb}(\eta\text{-C},N\text{-4-MeC}_5\text{H}_4\text{N})]$ (**2**-4-pic) by $[(\text{silox})_3\text{Ta}]^{[2]}$ in the presence of **2**-COT afforded $[(\text{silox})_3\text{Ta}(\eta\text{-4-pic})]$ and burgundy, crystalline $[(\text{silox})_3\text{Nb}]_2(\eta\text{-}1,2;\eta\text{-}5,6\text{-C}_8\text{H}_8)$ (**2**-COT, 33 %, Scheme 1). The synthesis of **2**-COT must occur under mild conditions to avoid further reaction (vide infra). An X-ray crystal structure determination of **2**-COT^[4,5] revealed the $[(\text{silox})_3\text{Nb}]$ moieties ($d(\text{Nb}-\text{C}) = 2.20(5) \text{ \AA}$ (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 **2**-COT in unreactive hydrocarbon solvents prevented spectral characterization.

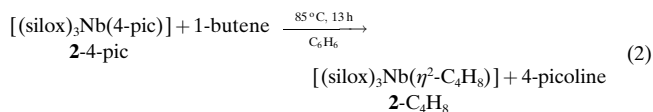
Upon thermolysis of two equivalents of $[(\text{silox})_3\text{Nb}(\eta\text{-C},N\text{-4-MeC}_5\text{H}_4\text{N})]$ (**2**-4-pic) and COT, **2**-COT and presumably **2**-COT were generated in situ, and dehydrogenation led to the gold-brown cyclooctatriene^[8] complex, $[(\text{silox})_3\text{Nb}]_2(\eta\text{-}1,2;\eta\text{-}5,6\text{-C}_8\text{H}_6)$ (**4**; Scheme 1). Although **4** was isolated in 50 % yield, ^1H 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, $[(\text{silox})_3\text{Nb}(\eta^2\text{-C}_4\text{H}_8)]$ (**2**-

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Scheme 1. Synthesis of 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.



Direct thermolysis of 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 ($d(\text{Nb}-\text{C}) = 2.091(8)$, $2.092(9)$ Å; $d(\text{C}-\text{C}) = 1.364(14)$ Å) is distinct from

5,6-alkene binding ($d(\text{Nb}-\text{C}) = 2.153(10)$, $2.177(9)$ Å; $d(\text{C}-\text{C}) = 1.335(12)$ Å) as the near planarity of the C8-C1-Nb-C2-C3 atoms attests.

The reversibility of the 2_2 -COT $\rightarrow$ 4 conversion was probed by thermolysis of 4 under H_2 . Instead, dihydrogen catalyzed the rearrangement of 4 to the orange alkydine-yne complex, $[(\text{silox})_3\text{Nb}]_2(\eta^1;\eta^2\text{-4,5-C}_8\text{H}_6)$ (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 ^1H 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 ($d(\text{Nb}-\text{C}) = 2.056(10)$, $2.145(11)$ Å), the niobium-alkylidene bond length of $1.971(10)$ Å is normal,^[1, 11] and the methylene is a substituent on the alkydine moiety.

When $[(\text{silox})_3\text{Nb}]_2(\eta^1;\eta^2\text{-4,5-C}_8\text{H}_5\text{D})$ (6-D) was synthesized from 4 and D_2 in a sealed tube, its ^1H NMR spectrum revealed that the intensity of the methylene resonance at $\delta = 4.70$ was halved, consistent with the incorporation of one deuterium atom. The overlapping

doublet of triplets at $\delta = 6.31$ 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 $\delta = 4.42$ (C_6D_6). Variable-temperature ^1H 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 alkydine 6 (see Scheme 1,). The hydrogenation of 4 may occur through a

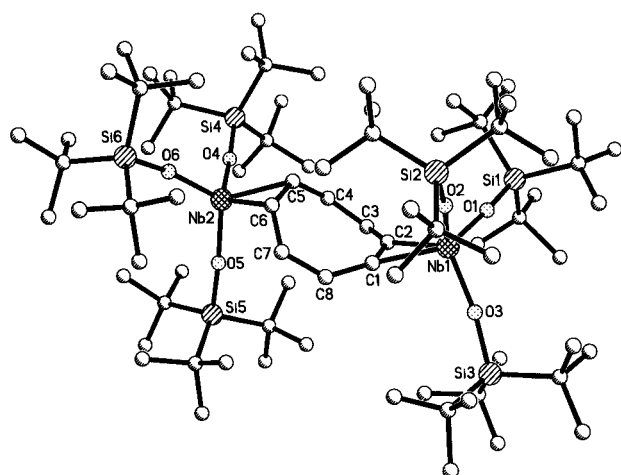


Figure 1. Molecular structure of 4. Selected distances [Å] and angles [$^\circ$]: Nb1-O 1.903(31) av, Nb2-O 1.912(47) av; Nb1-C1-C8 150.9(7), Nb1-C2-C3 152.3(8), Nb1-C1-C2 71.4(5), Nb1-C2-C1 71.4(5), C2-C1-C8 136.7(9), C1-C2-C3 135.7(9), Nb2-C5-C4 111.2(6), Nb2-C6-C7 124.3, Nb2-C5-C6 72.6(6), Nb2-C6-C5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

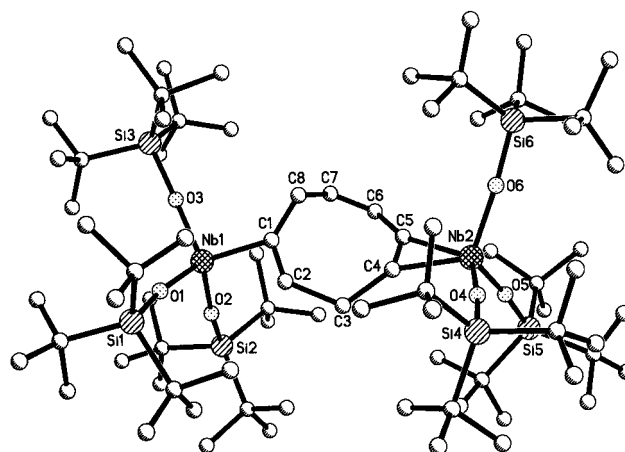
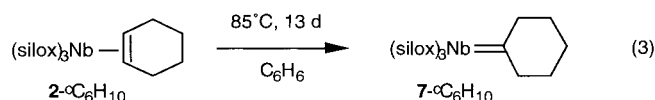


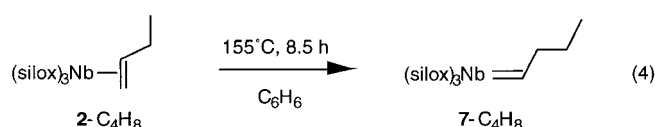
Figure 2. Molecular structure of 6; C8 is the methylene group. Selected distances [Å] and angles [$^\circ$]: Nb1-O 1.897(23) av, Nb2-O 1.900(30) av; Nb1-C1-C2 107.0(8), Nb1-C1-C8 129.2(8), C1-C8-C7 108.5(9), Nb2-C4-C3 149.4(8), Nb2-C5-C6 156.8(8), Nb2-C4-C5 77.5(7), Nb2-C5-C4 69.3(7), C3-C4-C5 129.0(10),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

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 indistinguishable σ -bond metathesis path.

The COT dehydrogenation and rearrangement reactions prompted an investigation of simple olefin complexes. Extended thermolysis of $[(\text{silox})_3\text{Nb}(\eta^2\text{-}C_6H_{10})]$ (**2**- C_6H_{10} , [Eq. (1)], 40%) induced the rearrangement to the cyclohexylidene complex, $[(\text{silox})_3\text{Nb}=\text{C}(\text{CH}_2)_4\text{CH}_2]$ (**7**- C_6H_{10} , 69% yield) [Eq. (3)]. Likewise, rearrangement of 1-butene



complex $[(\text{silox})_3\text{Nb}(\eta^2\text{-}C_4H_8)]$ (**2**- C_4H_8) to the butylidene complex $[(\text{silox})_3\text{Nb}=\text{CH}(\text{CH}_2)_2\text{CH}_3]$ (**7**- C_4H_8) was evidenced [Eq. (4)]. Thermolyses under H_2 led to olefin hydrogenation.



As Scheme 1 indicates, a logical dehydrogenation sequence involves C–H bond activation of **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**-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 ($\angle \text{Nb-C-C} \sim \angle \text{C-C-H} \sim 112.5^\circ$); 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**-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** $\rightarrow$ **6**, **2**- C_4H_8 $\rightarrow$ **6**- C_4H_8 and **2**- C_6H_{10} $\rightarrow$ **6**- C_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 $[(\text{silox})_3\text{NbCl}_2]$ (**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. ^1H NMR (C_6D_6 , 23 °C, TMS): δ = 1.23 (s, 81 H; *t*Bu), 5.64 (s, 8 H; C_8H_8); $^{13}\text{C}\{^1\text{H}\}$ NMR: δ = 24.18 ($C(\text{CH}_3)_3$), 31.35 ($C(\text{CH}_3)_3$), 112.17 (HC); elemental analysis calcd (%) for $C_{44}H_{80}Si_3O_3Nb$: C 62.7, H 10.6; found: C 60.4, H 10.1.

2- C_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**- C_6H_{10} (600 mg, 40%) was obtained

from hexanes. ^1H NMR (400 MHz, C_6D_6 , 23 °C, TMS): δ = 1.25 (s, 81 H; *t*Bu), 1.50–1.86 (m, 4 H; C_7H_2), 2.38–2.66 (m, 4 H; C_7H_2), 2.78 (m, 2 H; C_8H); $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 23 °C): δ = 23.90 ($C(\text{CH}_3)_3$), 25.07 (C_7), 28.46 (C_8), 31.21 ($C(\text{CH}_3)_3$), 70.76 (C_8); 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-COT: A 25 mL vial was charged with a mixture of $[(\text{silox})_3\text{Nb}(\text{4-pic})]$ (**2**-4-pic) (209 mg, 0.252 mmol) and $[(\text{silox})_3\text{Ta}]$ (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**-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%). ^1H NMR (C_6D_6 , 23 °C, TMS): δ = 1.25 (s, 81 H; *t*Bu), 1.33 (s, 81 H; *t*Bu), 3.19 (s, 2 H, Nb(η^2 -CHCH)), 6.81 (m, 2 H; $-\text{CH}=\text{}$), 6.98 (m, 2 H; $-\text{CH}=\text{}$); $^{13}\text{C}\{^1\text{H}\}$ NMR: δ = 23.94 ($C(\text{CH}_3)_3$), 24.18 ($C(\text{CH}_3)_3$), 31.39 ($C(\text{CH}_3)_3$), 31.43 ($C(\text{CH}_3)_3$), 80.16 (Nb(η^2 -CHCH)), 125.42, 129.07 ($\text{CH}=\text{CH}$).

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. ^1H NMR (C_6D_6 , 23 °C, TMS): δ = 1.24 (s, 81 H; *t*Bu), 1.35 (t, 3 H; CH_3), 1.73 (m, 1 H; $\text{CH}_2=\text{CH}-$), 1.95 (dd, 1 H; $\text{CH}_2=\text{CH}$), 2.5 (m, 1 H; $\text{CH}_2=\text{CH}$), 2.69 (m, 2 H; CH_2); $^{13}\text{C}\{^1\text{H}\}$ NMR: δ = 21.14 (CH_3), 23.85 ($C(\text{CH}_3)_3$), 31.11 ($C(\text{CH}_3)_3$), 33.82 (CH_2), 70.12, 84.02 ($\text{CH}_2=\text{CH}$); elemental analysis calcd (%) for $C_{40}H_{80}Si_3O_3Nb$: 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%). ^1H NMR (C_6D_6 , 23 °C, TMS): δ = 1.27 (s, 81 H; *t*Bu), 1.32 (s, 81 H; *t*Bu), 4.70 (br d, 3J = 8 Hz, 2 H; CH_2), 6.31 (dt, 3J = 10, 8 Hz, 1 H; $\text{CH}_2\text{CH}=\text{}$), 7.20 (d, 3J = 10 Hz, 1 H; $-\text{CH}=\text{}$), 8.30 (d, 3J = 11 Hz, 1 H; Nb= $\text{CCH}=\text{CH}-$), 5.70 (d, 3J = 11 Hz, 1 H; $-\text{CH}=\text{}$); $^{13}\text{C}\{^1\text{H}\}$ NMR (C_6D_6 , 23 °C): δ = 23.36 ($C(\text{CH}_3)_3$), 23.45 ($C(\text{CH}_3)_3$), 30.68 ($C(\text{CH}_3)_3$), 30.90 ($C(\text{CH}_3)_3$), 41.82 (CH_2), 111.75, 132.34, 134.73, 137.43 ($-\text{C}=\text{}$), 206.63, 211.54 (NbCC).

7- C_6H_{10} : A 50 mL glass bomb charged with **2**- C_6H_{10} (600 mg, 0.732 mmol) and benzene (25 mL) was placed in an 85 °C bath for 13 days. Green **7**- C_6H_{10} (415 mg, 69%) was obtained from pentane. ^1H NMR (C_6D_6 , 23 °C, TMS): δ = 1.16 (m, 2 H; C_8H_2), 1.28 (s, 81 H; *t*Bu), 1.59 (m, 4 H; C_7H_2), 3.78 (m, 4 H; C_7H_2); $^{13}\text{C}\{^1\text{H}\}$ NMR: δ = 23.67 ($C(\text{CH}_3)_3$), 26.96 (C_8), 29.12 (C_7), 31.07 ($C(\text{CH}_3)_3$), 40.99 (C_8), C_8 not observed; elemental analysis calcd (%) for $C_{42}H_{91}Si_3O_3Nb$: 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 . ^1H NMR (C_6D_6 , 23 °C, TMS): δ = 0.86 (t, J = 7.2 Hz, 3 H; CH_3), 1.12 (m, 2 H; CH_2), 1.29 (s, 81 H; *t*Bu), 3.49 (m, J = 7.2 Hz, 2 H; CH_2), 8.17 (bs, 1 H; Nb= CH); $^{13}\text{C}\{^1\text{H}\}$ NMR: δ = 13.74 (CH_3), 26.71 (CH_2), 23.96 ($C(\text{CH}_3)_3$), 30.99 ($C(\text{CH}_3)_3$), 44.10 (CH_2), 249.0 (Nb= C , HMQC); elemental analysis calcd (%) for $C_{40}H_{80}Si_3O_3Nb$: C 60.4, H 11.3; found: C 60.2, H 11.4.

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- [4] **2**-COT: triclinic; $P\bar{1}$; a = 12.297(3), b = 12.424(3), c = 17.864(4) Å, α = 79.61(3), β = 83.19(3), γ = 78.57(3)°; V = 2621.5(9) Å³; Z = 2, $H_{97}C_{46}O_3Si_3Nb$; T = 173(2) K; λ = 0.71073; 9126 reflections, 5396

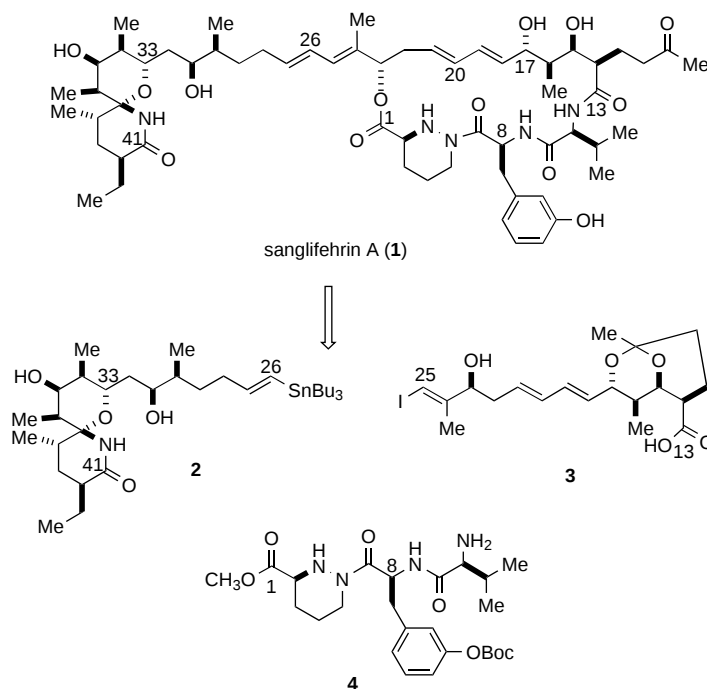
- independent; $R1 = 0.0793$ ($I > 2\sigma(I)$), $wR2 = 0.1523$; $\mu = 0.332 \text{ mm}^{-1}$ (SADABS); full-matrix, least-squares on F^2 .
- [5] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-163099 (**2**), 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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- [10] **6**· C_6H_6 : monoclinic, $P2_1/c$; $a = 24.6813(4)$, $b = 17.6046(3)$, $c = 25.4832(4) \text{ \AA}$, $\beta = 116.96(1)^\circ$; $V = 9869.5(3) \text{ \AA}^3$; $Z = 4$, $H_{171}C_{86}O_6Si_6Nb_2$; $T = 173(2) \text{ K}$; $\lambda = 0.71073$; 56059 reflections, 21816 independent; $R1 = 0.0864$ ($I > 2\sigma(I)$), 14073 reflections, $wR2 = 0.2119$; $\mu = 0.368 \text{ mm}^{-1}$ (SADABS); full-matrix, least-squares on F^2 .^[5]
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Enantioselective Total Synthesis of the Cyclophilin-Binding Immunosuppressive Agent Sanglifehrin A**

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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 immunosuppressive 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.



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