nulene moieties is concerted—whereas the singlet [4*k*]trannulenes are antiaromatic. The aromaticity of the singlet [2*k*]cyclacenes is also evidenced from the small calculated δ^1H chemical shift (0.4 – 2.6 ppm upfield), which arises from the perpendicular orientation of the hydrogens in the diatropically shielded region over the ring faces of the [4*k*]trannulene moieties.

According to the Hückel rule, 4*k* π-carbon rings like [4*k*]trannulenes tend to have two singly occupied molecular orbitals (SOMOs), so the singlet states are nonaromatic and unstable. Thus, in [2*k*]cyclacenes, two [4*k*]trannulene moieties tend to be coupled strongly through 2*k* bonds, as seen from somewhat short *r*(CC) values. Then, the two SOMOs of one [4*k*]trannulene moiety couple with the two SOMOs of the other. These four SOMOs are split into two occupied and two unoccupied MOs, which include the HOMO and LUMO, and are separated by ΔE_{gap}. The HOMO and LUMO, which have *k* nodal planes on each [4*k*]trannulene unit, are distinguished by one nodal plane between the two [4*k*]trannulenes (Figure 3). Since the coupling of two [4*k*]trannulene moieties by

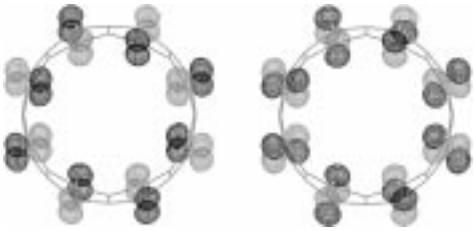

Figure 3. HOMO (left) and LUMO (right) of [8]cyclacene.

2*k* single-bond-like C–C bonds is somewhat weak, the ΔE_{gap} of [2*k*]cyclacenes is moderately small (≈1 eV), resulting in a very small $\Delta E_{S\text{-}T}$ value (≈1 kcal mol^{-1}). Thus, [2*k*]cyclacenes that are stabilized by strong aromaticity have interesting magnetic properties and behave as organic semiconductors.

We thus find that the cyclacene family invites experimental exploration. Potential applications include utilization as ionophores, receptors, organic semiconductors, organic magnetic materials, and molecular electronic devices. Owing to well-defined cavities or rims (radius = 0.3875*n* + 0.0664 Å), [*n*]cyclacenes with even values of *n* are suitable to capture cationic guests through cation – π interactions.[2a, 8] An understanding of the electronic structure and magnetic properties of [*n*]cyclacenes, the simplest building units of (*n*,0) carbon nanotubes, may be useful in designing short carbon nanotubes and investigating their growth mechanisms.

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Total Synthesis of the Marine Natural Product 7-Deoxy-okadaic Acid: A Potent Inhibitor of Serine/Threonine-Specific Protein Phosphatases**

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The naturally occurring marine toxin okadaic acid (**1**)[1] and its congeners present a widely recognized human health hazard due to their accumulation in edible shellfish.[2] Paradoxically, okadaic acid has also become an extremely valuable biomedical tool as the original member of a structurally diverse class of natural products that potently inhibit the serine/threonine-specific protein phosphatases 1 and 2A

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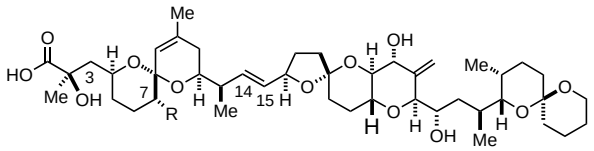
(PP-1 and PP-2A, respectively).[3] Elucidation of the molecular basis of enzyme binding and inhibition by these natural products[4] is an important objective given the increasing recognition of okadaic acid sensitive phosphatases in an astounding array of essential cellular processes and diseases.[5] Structure – activity studies of okadaic acid derivatives included the finding by Takai and co-workers that 7-deoxy-okadaic acid (**2**), isolated from the dinoflagellate *Prorocentrum lima*, closely mirrored the affinity of **1** towards PP-1 and PP-2A.[6] Hence, both **1** and **2** are among the most potent known inhibitors of the tumor suppressor PP-2A.[5c] In contrast to the parent compound, however, the availability of **2** from natural sources is extremely limited,[7] and no total synthesis has been reported previously.[8]

We describe here the first total synthesis of 7-deoxy-okadaic acid. This work corroborates the original structural assignment of **2**, provides an alternative source of this potent phosphatase inhibitor, and highlights the utility of our tricomponent coupling approach[8b] for the facile synthesis of structural variants of **1**.

The structure of **2** was assigned by Yasumoto and co-workers primarily on the basis of ^{1}H NMR spectroscopic and mass spectrometric data.[4b, 9] The omission of the single hydroxy group at C7 from **1** represents a minor structural variation in **2** that reportedly has little effect upon PP-1/PP-2A inhibitory activity. The presence of the free C7 hydroxy group of **1** is apparently also not required for high affinity

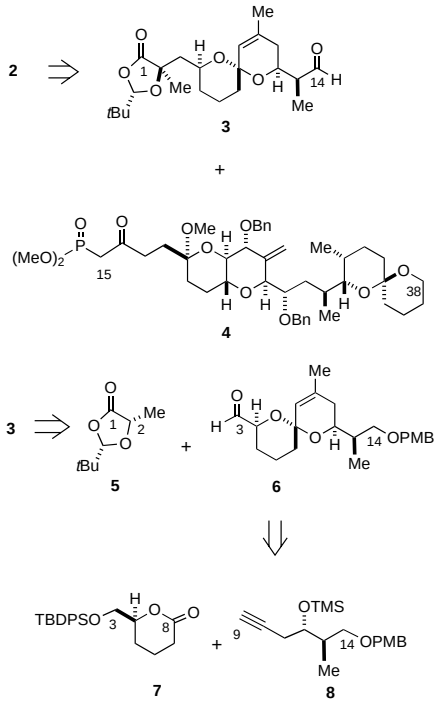


1: R = OH, Okadaic Acid
2: R = H, 7-Deoxy-okadaic Acid

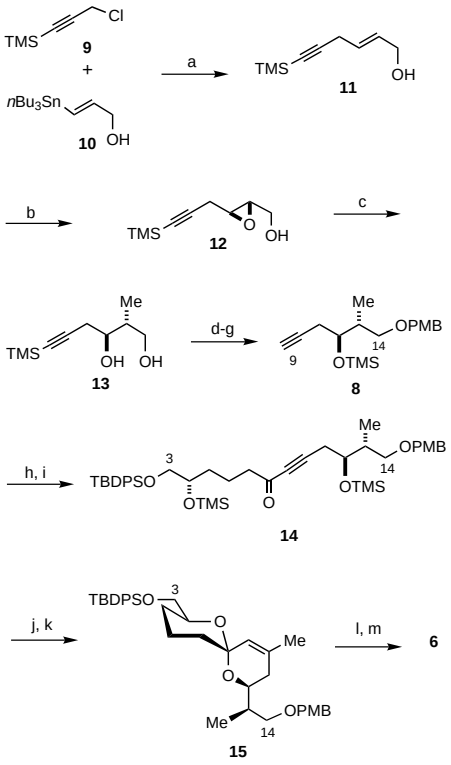
ligand binding to PP-2A.[6, 10] As we report here, however, the deletion of the C7 hydroxy group enhances the synthetic access to **2** over **1**. In particular, formation of the (8*R*)-spiroketal from the corresponding δ,δ'-dihydroxyenone, and the liberation of the final product by reductive scission of an advanced polybenzyl ether intermediate are facilitated in the absence of C7 functionalization. Hence, the development of a total synthesis of **2**, lacking the biologically dispensable and synthetically hampering C7 hydroxy group of **1**, was doubly warranted.

The synthesis of **2** relied upon the late-stage coupling of fully functionalized C1−C14 and C15−C38 intermediates. This convergent entry to the okadaic acid architecture was designed to facilitate the rapid assembly of okadaic acid analogues,[8b] and is particularly useful for those bearing structural variations in the C1−C14 domain. For the construction of **2**, the novel 7-deoxy-C1−C14 fragment **3** was coupled with the ketophosphonate **4**,[11] which represents the C15−C38 domain of both **1** and **2** (Scheme 1). The α-hydroxy-α-methyl carboxylate moiety of **3** was derived from Seebach's dioxolanone **5**,[12] and the C3−C14 spiroketal **6** was prepared from lactone **7** and alkyne **8**.

The synthesis of **2** began with an abbreviated approach to alkyne **8** (Scheme 2).[13] Silylated propargyl chloride **9**[14] and



Scheme 1. Retrosynthesis of 7-deoxy-okadaic acid (**2**).



Scheme 2. Synthesis of the 7-deoxy-okadaic acid intermediate **6**. a) $[Pd_2dba_3]\cdot CHCl_3$, PPh_3, THF, 50 °C, 39 %; b) $Ti(OiPr)_4$, L-(+)-diethyltartrate, *t*BuOOH, 85 % yield, 89 % *ee*; c) $Me_2CuCNLi_2$, Et_2O, 80 – 85 %; d) anisaldehyde dimethylacetal, camphorsulfonic acid, 93 %; e) $NaCNBH_3$, TFA, DMF, 82 %; f) TBAF, THF; g) TMSCl, Et_3N, CH_2Cl_2, 98 %, two steps; h) *n*BuLi, THF, then **7**; i) TMSCl, Et_3N, CH_2Cl_2, 84 %, two steps; j) Me_2CuLi, THF, 100 %; k) TsOH, benzene, 75 %; l) TBAF, THF; m) TPAP, NMO, CH_2Cl_2, 76 %, two steps. TMS = trimethylsilyl, TFA = trifluoroacetic acid, DMF = dimethylformamide, PMB = *p*-methoxybenzyl, TBAF = tetrabutylammonium fluoride, TsOH = *p*-toluenesulfonic acid, TPAP = tetrapropylammonium perruthenate, NMO = 4-methylmorpholine *N*-oxide.

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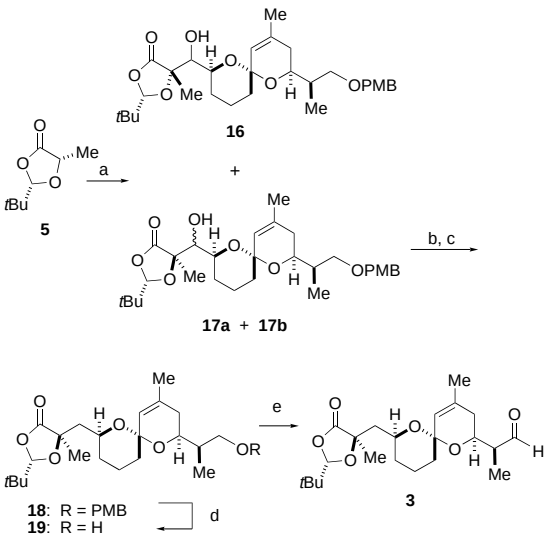
vinyl stannane **10**[15] underwent an unoptimized palladium-mediated coupling to afford allylic alcohol **11**.[16] Following a Sharpless asymmetric epoxidation[17] of **11** to provide **12**, regio- and stereoselective installation of the C13 methyl group was effected by hydroxy group directed opening of the epoxide ring in **12** with dimethylcuprate to give **13**.[18] Diol **13** was converted to its anisylidene derivative, which was treated with trifluoroacetic acid and sodium cyanoborohydride to induce regioselective reductive opening of the anisylidene to the secondary alcohol.[19] Clean desilylation of the alkyne followed by silylation of the secondary alcohol completed a concise synthesis of alkyne **8**. Deprotonation of **8** with *n*-butyllithium followed by reaction with lactone **7**[20] generated the corresponding δ-hydroxy ynone, which was converted into tris-silyl ether **14**. The C10 methyl group was then installed by a non-stereoselective conjugate 1,4-addition of lithium dimethylcuprate to the C≡C bond to generate a 1:1 (*E*,*Z*) mixture of enones in nearly quantitative yield. Upon treatment with TsOH in benzene at room temperature for 3 h, the mixture of enones converged to the thermodynamically favored spiroketal **15**. Considerably higher yields were obtained for this spiroketalization than for the analogous transformation in the synthesis of **1**.[21] The structure of **15** was confirmed at this stage by correlation with a deoxygenation product obtained from the corresponding (8*R*,7*R*)-7-benzyloxyspiroketal used in the total synthesis of **1**.[22] Desilylation of **15** and oxidation of the resultant alcohol gave aldehyde **6** in 13 steps and 10% overall yield from propargyl chloride **9** and vinyl stannane **10**.

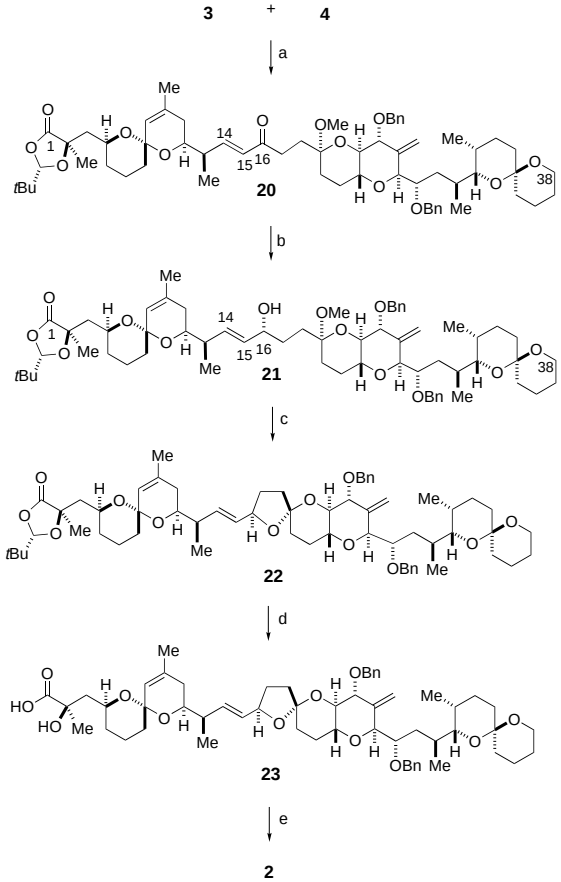
Completion of the synthesis of the C1–C14 fragment of 7-deoxy-okadaic acid required installation of a protected α-hydroxy-α-methyl carboxylate moiety. To this end, dioxolanone **5**[12] was deprotonated with LDA and then treated with aldehyde **6** to give a mixture of three chromatographically separable alkylation products **16**, **17a**, and **17b** in an approximate equimolar ratio (Scheme 3). Separate treatment



Scheme 3. Synthesis of the C1–C14 domain **3** of 7-deoxy-okadaic acid. a) LDA, THF, then **6**, ca. 2:1, (**17a** + **17b**):**16**, ca. 100% combined; b) NaH, CS_2, MeI, THF; c) nBu_3SnH, AIBN, toluene, 80 °C, 70%, two steps; d) DDQ, *t*BuOH, CH_2Cl_2, 79%; e) TPAP, NMO, CH_2Cl_2, 89%. LDA = lithium diisopropylamide, AIBN = 2,2′-azobisisobutyronitrile, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

of each of the alkylation products under Barton deoxygenation conditions[23] showed that **17a** and **17b** converged to the single product **18** upon deoxygenation, indicating that they were epimeric at the newly formed C3 center, whereas the product of deoxygenation of **16** was diastereomeric with **18**. Hence, **17a** and **17b** were assigned the (2*R*)-configuration based upon literature precedent[12, 21] which included the observation that a similar ratio (ca. 2:1) of (2*R*)- to (2*S*)-isomers was obtained in the synthesis of okadaic acid (**1**). Oxidative cleavage of the *p*-methoxybenzyl ether of **18** gave primary alcohol **19**, which was oxidized cleanly to aldehyde **3** by using TPAP/NMO[24] to complete the assembly of the C1–C14 intermediate in five steps and 32% yield from dioxolanone **5** and aldehyde **6**.

Paralleling the successful end game strategy used for the synthesis of **1**,[21] only five additional steps were required to complete the synthesis of 7-deoxy-okadaic acid. The first step involved joining[25] aldehyde **3** with β-ketophosphonate **4** to give (*E*)-enone **20** (Scheme 4). Stereoselective reduction of



Scheme 4. Convergent total synthesis of 7-deoxy-okadaic acid (**2**). a) LiCl, iPr_2NEt, CH_3CN, 76%; b) (*S*)-Me-CBS, $BH_3 \cdot DMS$, THF; c) TsOH, benzene, 55%, two steps; d) LiOH, THF, H_2O, ca. 100%; e) LiDBBP, THF, ca. 64%. Me-CBS = Corey–Bakshi–Shibata oxaborolidine, DMS = dimethylsulfide, LiDDBP = lithium di-*tert*-butylbiphenylide.

the ketone using Corey's reliable chiral oxaborolidine reagent[26] gave allylic alcohol **21**, which was treated with *p*-toluenesulfonic acid in benzene to trigger intramolecular transketalization to provide spiroketal **22**. Saponification of **22** simultaneously released the C1 carboxylate and C2

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hydroxy groups to yield hydroxy acid **23**. Finally, cleavage of the two benzyl ethers of **23** was accomplished cleanly and with no evidence of overreduction using lithium di-*tert*-butylbiphenylide (LiDBBP)[27] in THF to provide **2**. The ^{1}H NMR, HR-FAB-MS, and HPLC/MS of synthetic **2** matched those of the natural product.[28] Remarkably, trihydroxycarboxylic acid **2** was only slightly more polar than hydroxy acid **23** on silica gel,[29] which may reflect the donation of an intramolecular hydrogen bond from the newly liberated C24 hydroxy group to the carboxylate moiety in a cyclic conformation of **2** which is similar to that of **1** (Figure 1).[1, 30] Accordingly, the ^{1}H NMR

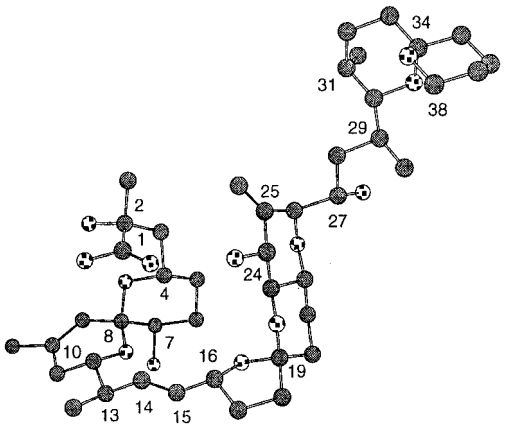

Figure 1. Conformational model for **1**.[1]

spectra (500 MHz, $CDCl_3$) of both **1**[31] and synthetic **2** displayed similar exchangeable proton resonances at $\delta = 2.5$ and 5.9 (**1**) or 6.2 (**2**), the latter downfield pair being indicative of intramolecular hydrogen bonding (Figure 2). Hence, unlike

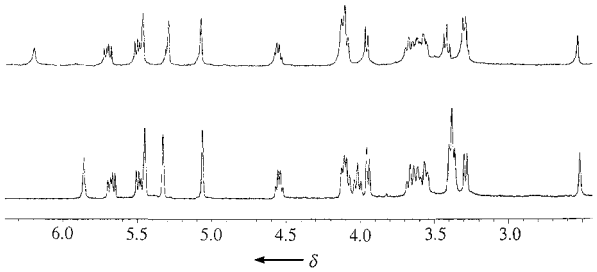

Figure 2. Partial ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C, Me_4Si) spectra of **1**[31] and synthetic **2**.

the C2,[4a,b] C24,[30] and C27[32] hydroxy groups of **1**, the C7 hydroxy moiety appears to contribute little to either the solution phase conformation or phosphatase inhibitory activity.

The total synthesis of **2** capitalizes on our recently established convergent synthetic approach to **1** to corroborate the structure of the potent phosphatase inhibitor isolated from *P. lima* by Yasumoto and co-workers. This work departs from previous synthetic efforts in the utilization of abbreviated syntheses of C3–C8 and C9–C14 intermediates, a substantially more efficient synthesis of the C3–C14 spiroketal, and an unproblematic final deprotection. The enhanced synthetic access to **2** over **1**, combined with the similar structural and enzymatic inhibitory characteristics of both, supports the development and use of okadaic acid analogues in further studies involving biologically important okadaic acid sensitive phosphatases.[5]

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[28] Synthetic **2** was obtained as an amorphous white solid after purification by preparative TLC:[29] ^{1}H NMR (500 MHz, $CDCl_3$) $\delta =$ 6.17 (br s, 1H), 5.67 (dd, $J = 15.5$, 9.0 Hz, 1H), 5.46 (dd, $J = 15.5$, 8.5 Hz, 1H), 5.43 (s, 1H), 5.26 (s, 1H), 5.04 (s, 1H), 4.52 (q, $J = 8.0$ Hz, 1H), 4.07 (m, 3H), 3.93 (d, $J = 9.0$ Hz, 1H), 3.38 (t, $J = 10.0$ Hz, 1H), 3.27 (br d, $J = 10.0$ Hz, 2H), 2.22–2.00 (m, 4H), 2.00–0.82 (m, 29H), 1.69 (s, 3H), 1.34 (s, 3H), 1.03 (d, $J = 6.5$ Hz, 3H), 0.97 (d, $J = 6.5$ Hz, 3H), 0.90 (d, $J = 7.0$ Hz, 3H); HR-FAB-MS: calcd for $C_{45}H_{68}O_{12}$ $[M+H]^+$ 789.4789, found 789.4751; HPLC/MS[7] (C_{18} 3.5 μm, 2.1 × 150 mm, CH_3CN/H_2O/acetic acid, 70:30:0.05, 0.2 mL min^{-1}, 40 °C; ES$^-$ (Micromass Quattro, 70 eV): *m*/*z*: 787.5 $[M-H]^-$) $t_R = 14.55$ min, co-eluted with naturally occurring **2**. For HPLC traces and ^{1}H NMR spectra of synthetic (partial spectrum is shown in Figure 2) and naturally occurring **2** see Supporting Information.
[29] TLC (E. Merck Silica gel 60 F_{254}s, 0.2 mm, Art. 115696, hexanes/ethyl acetate/acetic acid, 1:1:0.05): R_f data for compounds **2**, 0.47; **23**, 0.58; **1**, 0.27; 7,24,27-tri-*O*-benzyl-**1**,[21] 0.69.
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Synthesis and Structure of the First Lanthanide Complex with the Bridging, Antiaromatic 2,2′-Bipyridine Dianion: $[\{Yb(\mu_2\text{-}N_2C_{10}H_8)(thf)_2\}_3]$**

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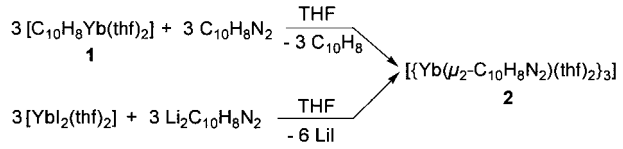
Neutral 2,2′-bipyridine (bipy) has been used for decades in coordination chemistry as a chelating N-donor ligand. In the last few years, a number of interesting reactions of bipy complexes of d-transition metals has been reported involving electron and proton transfer processes. In these reactions the bipy ligand is suggested to act as a kind of an electron reservoir.[1] The formation of bipy$^{\bullet-}$ radical anions and also of bipy^{2-} dianions from bipy and one or more equivalents of lithium was briefly described in 1968.[2] Some lanthanide complexes with bipy$^{\bullet-}$ radical anions as ligands have been well characterized by spectroscopic methods and by structure determination.[3] During the refereeing of our paper the first sodium complexes of the 2.2′-bipyridine dianion were described by Bock and Lehn.[4]

Here, we report the first lanthanide complex containing the antiaromatic bipy^{2-} as a ligand. Trimeric $[\{Yb(\mu_2\text{-}N_2C_{10}H_8)(thf)_2\}_3]$ (**2**) is formed by reduction of 2,2′-bipyridine with ytterbium naphthalene $[C_{10}H_8Yb(thf)_2]$ (**1**),[5] as well as by the reaction of $[YbI_2(thf)_2]$ with $[Li_2(bipy)]$ in THF at room temperature (Scheme 1). Complex **2** crystallized from the



Scheme 1. Synthesis of **2**.

concentrated dark green solutions as large, almost black crystals (70 to 80% yield), which are extremely sensitive to air and moisture and decompose without melting at 160 °C. The solubility of **2** in THF is low at room temperature, but increases significantly upon heating. The complex is insoluble in toluene and diethyl ether. As expected the complex is diamagnetic and does not display ESR signals.

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