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[2 + 2] Photochemical Cycloaddition/Ring Opening of 6-Alkenyl-2,3-dihydro-4-pyridones

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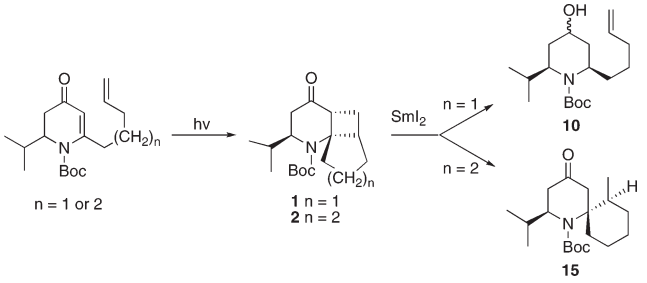


During the course of a study aimed at constructing azaspirocycles from 2,3-dihydro-4-pyridones, an unexpected product was obtained in the SET ring-opening reaction of photocycloadduct **1**. Differences in reactivity between homologues **1** and **2** were observed in the presence of SmI_2. Tricyclic ketone **2** afforded azaspiro[5.5]undecane **15** when treated with SmI_2; however, when ketone **1** was submitted to similar reaction conditions a double ring-opening/reduction sequence gave *cis*-piperidinol **10**.

Azaspirocycle natural products have garnered considerable interest from the synthetic community due to their unique molecular architecture and interesting biological properties.[1,2] A variety of methods for accessing the core spiro ring system have been developed.[3,4] While exploring

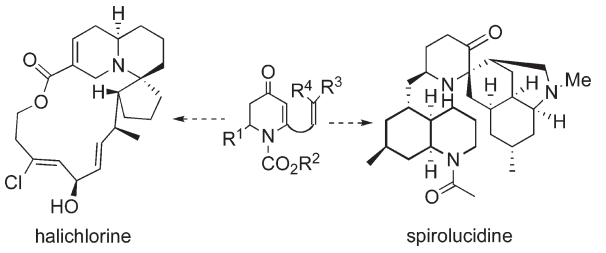
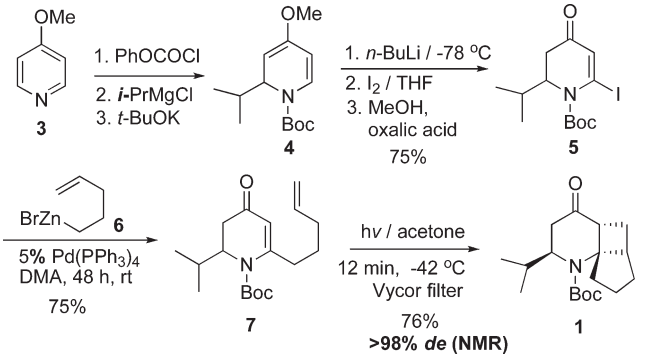


FIGURE 1. Proposed [2 + 2] photocyclization route to azaspirocycle natural products.

modular routes to α-substituted azaspirocycles, which might be applied to natural product synthesis (Figure 1), we investigated a model study involving a photocycloaddition/ring-opening sequence commencing with olefin-tethered 2,3-dihydro-4-pyridones. Irradiation of these dihydropyridones induces a [2 + 2] cycloaddition to give an α-ketocyclobutane.[5,6] A subsequent homolytic cyclobutane cleavage could lead to the desired azaspirocycles. It was anticipated, based on previous investigations by this group,[6] that both [4.5] and [5.5] azaspiro ring systems could be accessed from dihydro-4-pyridone intermediates by employing olefin side chains of appropriate length.

SCHEME 1. Preparation of Photoadduct 1



Synthesis of the olefin-tethered dihydro-4-pyridone **7** commenced with the addition of isopropylmagnesium chloride to the *N*-(phenoxycarbonyl)pyridinium salt of 4-methoxypyridine[7] to give 1,2-dihydropyridine **4** after carbamate exchange with *t*-BuOK[8] (Scheme 1). Lithiation of **4** followed by iodination afforded iododihydropyridone **5** after exposure to oxalic acid in methanol.[6b,8] Next, iodide **5** was submitted to a Negishi coupling reaction with organozinc[9] **6** to give the 2,6-disubstituted dihydropyridone **7** in good yield.[10]

Initial attempts to photocyclize (450 W Hanovia Hg lamp) **7** in acetonitrile[6b] were unfruitful, resulting in decomposition of the starting material. However, when the solvent was

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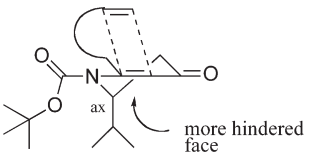


FIGURE 2. $A^{(1,3)}$ strain induced facialselective [2 + 2] photocycloaddition.

changed to acetone, a 76% yield of **1** was obtained after 12 min of irradiation through a Vycor filter (> 210 nm) at −42 °C. The excellent stereoselectivity of the photocycloaddition arises from the C-2 isopropyl group residing in a pseudoaxial orientation as a consequence of $A^{(1,3)}$ strain[6,11] with the *N*-Boc group (Figure 2). Consequently, the olefin approaches the enone from the less hindered π face, affording tricycle **1** as a single diastereomer.

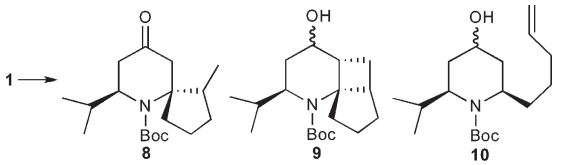
When ketone **1** was treated with SmI_2 in the absence of a proton donor,[1d] (entries 1 and 2), only unreacted starting material was returned (Table 1). Addition of methanol[12] to the reaction mixture (entries 4 and 5) resulted in reduction to tricyclic alcohol **9** (mixture of diastereomers). It was at this point that we first observed the formation of **10** as a minor product (ca. 10%). When HMPA and *t*-butanol were substituted for DMPU and methanol, the pentenyl-4-piperidinol **10** was obtained as the sole product (entry 8). Unexpectedly, tricyclic ketone **1** had undergone a double ring opening/reduction to terminal olefin **10** (mixture of diastereomers). It is noteworthy that other SET reagents, including Li^0, Zn^0, and Ti^0 all resulted in the recovery of **1**. In order to confirm the structure of **10**, the diastereomeric alcohols were first oxidized to piperidone **11** (Scheme 2). Studies using 1D and 2D NMR, coupled with mass spectrometry, are supportive of the proposed structure. NOE studies on **11** were not definitive, thus the relative stereochemistry needed to be ascertained. Accordingly, piperidone **12** was converted to **11** via 1,4-addition of an organocopper reagent, a reaction that is precedented to give *cis*-piperidinones.[13] Both piperidone samples showed identical R_f values, molecular ions, and ^1H and ^{13}C NMR spectral data.

The relative stereochemistry was finally established unequivocally by removal of the Boc group of **11** giving free amine **13**; a NOESY experiment on **13** confirmed the *cis* stereochemistry of **11** and suggests that the radical ring opening was proceeding with conservation of stereochemistry at C-6.

In light of our previous studies,[1d,6a] which showed that tricyclic ketones related to **1** but possessing a six-membered cycloalkane ring were easily transformed to azaspirocycles, we felt that a direct comparison between **1** and its higher homologue **2** under the action of SmI_2 would be informative. At this point, it was unclear whether the smaller cyclopentane ring was responsible for olefin formation. Accordingly, tricyclic ketone **2** was prepared in similar fashion to **1** (Scheme 3). Treatment of **2** with 4.1 equiv of SmI_2 in a THF/DMPU solvent system afforded spirocycle **15** in 81% yield. X-ray crystallographic analysis verified the relative stereochemistry of **15**. This result suggests that the size of the carbocyclic ring is dictating the reaction pathway.

On the basis of these findings, a mechanism for the formation of olefin **10** is proposed (Scheme 4). Ketyl **16** is generated after electron transfer from SmI_2. Homolytic C−C bond cleavage of the cyclobutane ring in **16** gives samarium enolate **17**, which undergoes protonation and radical collapse to form radical olefin **18**. Another electron transfer from SmI_2 generates the more thermodynamically stable carbanion **19**. Subsequent protonation and reduction give **10**.[14]

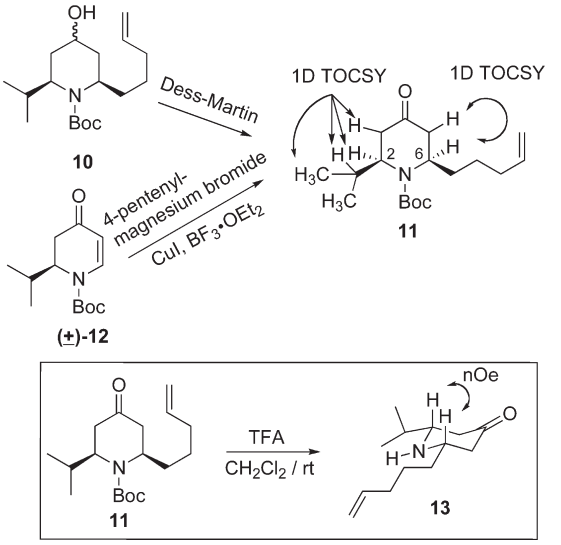
TABLE 1. Attempted Formation of Azaspiro[4.5]decane 8



entry	conditions	result[a]
1	2 equiv SmI_2/THF DMPU/25 °C/30 min	**1**
2	3.8 equiv SmI_2/THF DMPU/25 °C/1 h	**1**
3	4.0 equiv SmI_2/THF DMPU/2 equiv *t*-BuOH	**1** (trace of **10**)
4	4 equiv SmI_2/2 equiv MeOH DMPU/THF	**9** (trace of **10**)
5	3 equiv SmI_2/2 equiv MeOH DMPU/THF/25 °C	**9** (trace of **10**)
6	6.0 equiv SmI_2/THF HMPA	**1**
7	3 equiv SmI_2/HMPA THF/1 drop *t*-BuOH 25 °C/1 h	**9** + **10**
8	2.6 equiv SmI_2 THF/HMPA/25 °C 4 equiv *t*-BuOH	**10**

[a]Reaction result determined by ^1H NMR analysis. Product **8** was not observed. Alcohols **9** and **10** were formed as a mixture of diastereomers.

SCHEME 2. Stereochemical Confirmation of Piperidinol 10 via Ketone 11



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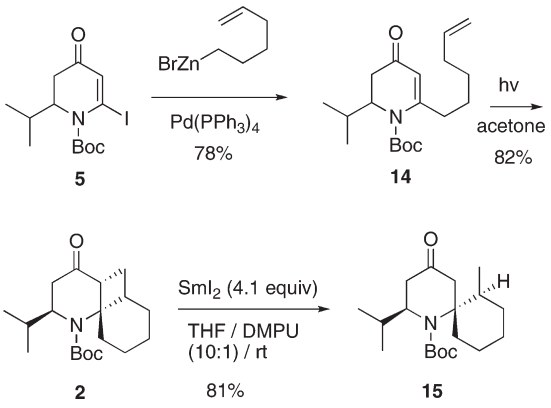
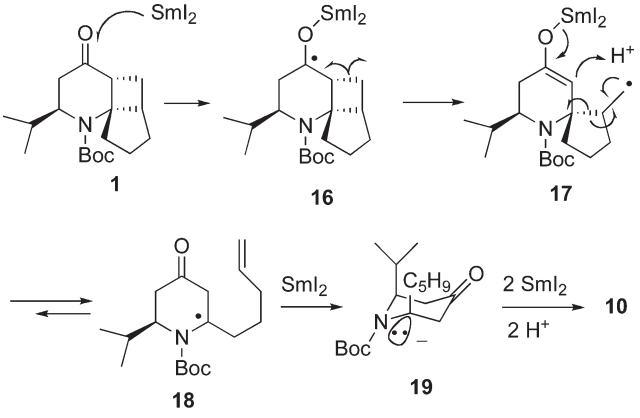
SCHEME 3. Preparation of Spirocycle 15



SCHEME 4. Proposed Mechanism for the Formation of 10



In summary, the intramolecular [2 + 2] photochemical cycloaddition has been successfully performed on two new dihydropyridones. Both reactions proceeded with excellent stereochemical control, demonstrating that an axial C-2 isopropyl group is of sufficient steric bulk to effectively shield one face of the enone system. Additionally, conditions have been developed for a high-yielding, palladium-catalyzed cross-coupling of organozinc reagents with 6-iodo-2,3-dihydro-4-pyridones, providing access to a versatile enone−olefin dihydropyridone system. The cross-coupled products are well suited for a wide array of chemical transformations.

Both α-ketocyclobutanes **1** and **2** were submitted to SET reactions. When treated with SmI_2, α-ketocyclobutane **2** underwent facile ring opening to azaspiro[5.5]undecane **15**. Conversely, the lower homologue **1**, when exposed to SmI_2, afforded *cis*-piperidinol **10**. The reason for this reactivity difference is unknown, although it is suggested that differences in orbital alignments of the primary radical intermediates may be controlling the reaction pathways.

Experimental Section

7-Isopropyl-5-oxo-octahydro-8-azacyclopenta[1,4]cyclobuta-[1,2]benzene-8-carboxylic acid *tert*-butyl ester (1). A solution of enone **6** (105 mg, 0.34 mmol) in acetone (250 mL) was placed in a standard photochemical reactor equipped with an immersion well containing a 450 W Hanovia mercury lamp and degassed with argon for 30 min with stirring. The solution was cooled to −42 °C, irradiated for 12 min, and allowed to warm to rt. The solvent was removed in vacuo, and the crude residue was purified by radial PLC (SiO_2; gradient elution, 100% hexanes; 5% EtOAc/hexanes; 10% EtOAc/hexanes) to provide 72 mg (69%) of tricyclic ketone **1** as a colorless oil: IR (neat) 2970, 2873, 1687, 1472, 1381, 1366, 1338, 1293, 1175 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.35 and 4.09 (br s, due to rotamers, 1 H), 2.79−2.58 (m, 4 H), 2.15−1.76 (m, 6 H), 1.55−1.35 (m, 10 H), 0.96−0.83 (m, 8 H); ^{13}C (75 MHz, $CDCl_3$) δ 211.3, 154.9, and 154.5 (due to rotamers), 80.6 and 80.3 (due to rotamers), 70.6, 66.8, 61.3, 58.7, 58.1, and 57.9 (due to rotamers), 53.6, 48.4, 46.2, 43.2, 42.4, 42.8, and 41.3 (due to rotamers), 39.2, 38.7, 38.1, 33.4, 32.4, and 32.1 (due to rotamers), 31.5, 28.9, and 28.7 (due to rotamers), 26.5, 26.2, 25.0, 24.4, 20.4, and 20.0 (due to rotamers), 19.5 and 19.4 (due to rotamers); HRMS $(M + Na)^+$ calcd for $C_{18}H_{29}NO_3Na$ 330.2039, found 330.2049.

2-Isopropyl-4-oxodecahydro-1-azacyclobuta[1,2:1,4]dibenzene-1-carboxylic acid *tert*-butyl ester (2). A solution of enone **14** (90 mg, 0.28 mmol) in acetone (250 mL) was placed in a standard photochemical reactor equipped with an immersion well containing a 450 W Hanovia mercury lamp. The solution was degassed with argon for 30 min with stirring. The reaction was cooled to −42 °C, irradiated for 12 min, allowed to warm to rt, and concentrated in vacuo. The crude product was purified using radial PLC (non-UV-active, collected in 30 mL portions) (SiO_2; gradient elution, 100% hexanes; 5%EtOAc/hexanes) to provide 82 mg (82%) of pure cyclobutanone **2** as a colorless oil: IR (neat) 2972, 1687, 1454, 1378, 1293, 1251, 1173, 1126, 1011 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.45 and 4.19 (pair of br s, due to rotamers, 1 H), 3.08−2.80 (m, 2 H), 2.70−2.50 (m, 2 H), 2.35−2.10 (m, 3 H), 2.02−1.70 (m, 2 H), 1.60−1.25 (m, 13 H), 0.096 (m, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.2, 155.6, and 153.7 (due to rotamers), 80.2, 61.1, 60.5, and 59.7 (due to rotamers), 46.0, 43.3, 41.2, 37.6, 33.1, and 32.4 (due to rotamers), 28.9, 27.4, 21.6, 20.5, and 19.8 (due to rotamers), 18.5; HRMS calcd for $C_{19}H_{31}NO_3$ 321.2304, found 321.2308.

2-Isopropyl-4-oxo-6-pent-4-enyl-3,4-dihydro-2*H*-pyridine-1-carboxylic acid *tert*-butyl ester (7). To 7.5 mL of DMA containing zinc dust (Nanozinc, Aldrich, 753 mg, 11.5 mmol) was added I_2 (97 mg, 0.38 mmol). After stirring at rt for 30 min, 1-bromopentene (0.88 mL, 7.5 mmol) was added (neat) via syringe. The reaction temperature was raised to 90 °C for 20 min, then stirred at 45 °C for 12 h, after which time TLC showed complete disappearance of 1-bromopentene. The organozinc solution was cooled to rt, and a DMA solution (5 mL) of 6-iodo-2,3-dihydropyridone **5** (200 mg, 0.54 mmol) was added via syringe, followed by tetrakis(triphenylphosphine)palladium (22 mg, 0.019 mmol). After stirring for 45 h at rt, water (5 mL) was added, and the mixture was extracted with diethyl ether. The combined ether extracts were washed with water and brine and dried over $MgSO_4$. Concentration in vacuo provided the crude product, which was purified by radial PLC (SiO_2; gradient elution, 100% hexanes; 5% EtOAc/hexanes; 10% EtOAc/hexanes) to give 105 mg (75%) of **6** as a colorless oil: IR (neat) 2920, 2836, 1643, 1028 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.75 (m, 1 H), 5.37 (s, 1 H), 5.03−4.94 (m, 2 H), 4.28 (ddd, J = 10.2, 5.6, 1.8 Hz, 1 H), 3.00 (m, 1 H), 2.70 (dd, J = 17.3, 5.6 Hz, 1 H), 2.51 (m, 1 H), 2.34 (m, 1 H), 2.05 (m, 3 H), 1.57 (m, 1 H), 1.50 (s, 9 H), 0.90 (d, J = 6.8 Hz, 3 H), 0.87 (d, J = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.2, 159.2, 152.8, 142.7, 137.9, 115.6, 113.0, 82.9, 62.5, 39.8, 38.4, 35.9, 33.5, 28.2, 27.4, 20.6, 19.7, 19.2; HRMS calcd for $C_{18}H_{29}NO_3$ 307.2147, found 307.2139.

2-Isopropyl-4-oxo-6-pent-4-enylpiperidine-1-carboxylic acid *tert*-butyl ester (11). To THF (8 mL) containing CuI (850 mg, 4.5 mmol) at −65 °C was added 4-pentenylmagnesium bromide (5.3 mmol in 4 mL of THF) dropwise via syringe. After 1.5 h, the

(14) The conformation shown for carbanion **19** is assumed to be the most stable chair due to $A^{1,3}$ strain; see refs 6 and 11.

reaction was cooled to −78 °C and $BF_3 \cdot OEt_2$ (0.5 mL, 4 mmol) was added dropwise. After 10 min, 2,3-dihydropyridone (±)-**12** (345 mg, 1.44 mmol) in THF (3 mL) was added dropwise over a 15 min period. After 10 min, TLC showed no starting material, and the reaction was quenched with an aqueous solution of 1:1 NH_4OH/NH_4Cl (10 mL) and then warmed to rt. The aqueous mixture was extracted with diethyl ether, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude product. Column chromatography (SiO_2; gradient elution, 100% hexanes; 5% EtOAc/hexanes; 7.5% EtOAc/hexanes; 10% EtOAc/hexanes) gave 360 mg (81%) of piperidone **11** as a colorless oil: IR (neat) 3075, 2971, 2931, 2873, 1721, 1456 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.77 (m, 1 H), 4.97 (m, 2 H), 4.46 (br s, 1 H), 4.26 (br s, 1 H), 2.65 (m, 1 H), 2.55 (d, J = 5.2 Hz, 2 H), 2.34 (dd, J = 15.4, 4.6 Hz, 1 H), 2.06 (m, 2 H), 1.81 (m, 2 H), 1.47 (s, 9 H), 1.44−1.37 (m, 3 H), 0.97 (d, J = 6.4 Hz, 3 H), 0.91 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 155.4, 138.3, 115.0, 80.2, 58.6, 52.7, 43.3, 41.9, 36.5, 33.5, 32.9, 28.5, 26.2, 20.5, 20.2; HRMS calcd for $C_{18}H_{31}NO_3$ 309.2304, found 309.2300.

2-Isopropyl-7-methyl-4-oxo-1-azaspiro[5.5]undecane-1-carboxylic acid *tert*-butyl ester (15). To a solution of THF (15 mL) and DMPU (1.5 mL) containing ketone **2** (49 mg, 0.15 mmol) was added SmI_2 (3.2 mL, 0.32 mmol 0.1 M in THF) dropwise at rt. After the purple color of the solution dissipated (ca. 20 min), more SmI_2 (3.0 mL, 0.30 mmol) was added. When the purple color again dissipated, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (3 mL), and the mixture was extracted with diethyl ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give the crude product. Purification by radial PLC (SiO_2; 100% hexanes, 5% EtOAc/hexanes, 10% EtOAc/hexanes) gave 40 mg (81%) of **15** as a colorless oil: IR (neat) 2966, 2972, 2874, 1720, 1689, 1464, 1366, 1345 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.30 (br s, 1 H), 3.01 (d, J = 18.4 Hz, 1 H), 2.62 (m, 2 H), 2.33 (d, J = 18.4 Hz, 1 H), 1.82 (m, 1 H), 1.65−1.50 (m, 8 H), 1.49 (s, 9 H), 1.25 (m, 1 H), 1.05 (d, J = 6.8 Hz, 3 H), 0.88 (d, J = 6.8 Hz, 3 H), 0.70 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.8, 154.4, 80.2, 63.2, 57.8, 44.3, 41.6, 38.5, 34.1, 31.6, 28.8, 25.6, 22.9, 20.9, 20.6, 17.0; HRMS calcd for $C_{19}H_{33}NO_3$ 323.2460, found 323.2455.

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Supporting Information Available: Experimental procedures and characterization for **4**, **5**, **10**, **13**, and **14**. NMR spectra for **1**, **2**, **4**, **5**, **7**, **10**, **11**, and **13**−**15**, and ORTEP plot and X-ray crystal data (CIF) for **15**. This material is available free of charge via the Internet at http://pubs.acs.org.