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3 Step Synthesis of 3-Methylindole (Skatole) via Hydroboration and Cyclization

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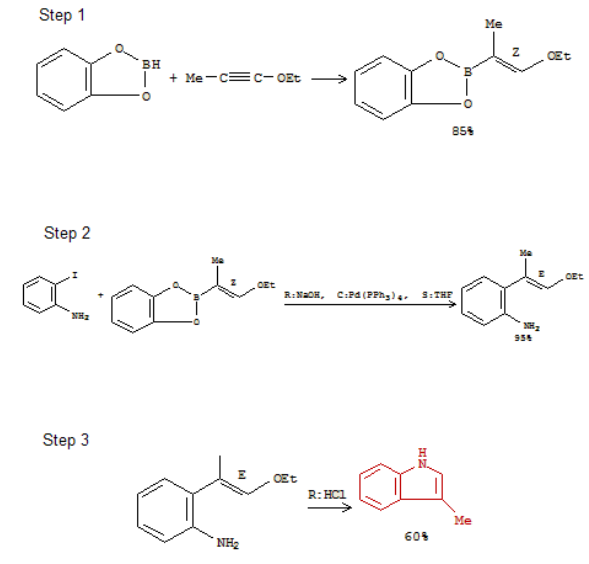
The informal name for the compound we are proposing to synthesize is skatole. The word skatole is derived from the Greek word skato, which means dung. This compound can be found in mammalian feces and has a sharp odor. Ironically, in low concentration, skatole has a flowery scent and is used in the manufacturing of perfumes. Another interesting fact about this molecule is that it has been found to cause pulmonary edema in goats, sheep, and several rodents, such as mice and rats. Besides the aforementioned intriguing properties, we are also interested in synthesizing this compound because of its intrinsic chemical structure. It is an aromatic compound and as such can be detected using UV-Vis spectroscopy. We will also be able to use IR Spectroscopy to positively identify the molecule at the completion of the synthesis, for example the sharp N-H peak at 3500-3300 cm^{-1}. In addition to the above mentioned techniques, H-NMR can also be used to identify the product. In addition, we also believe the characteristic smell of skatole will also assist us in its positive identification.



Step 1

Synthetic transformation 1:
Note: the scale was modified in order to produce 0.5 g of the desired product. Everything was scaled up by a factor of 35.7143.

1-ethoxy-1-alkyne (1.428 mol) is added to a dry 250 ml-flask equipped with a magnetic stirring bar and a septum inlet. 1,3,2-Benzodioxiborole (142.86 ml, 1.286 mol) is added slowly by a buret. This mixture is heated for 5 hours at 70°C. Distillation under reduced pressure gives the product 2-(1-ethoxy-1-propen-2-yl)-1,3,2-benzodioxaborole as a gelatinous oil.

Honors Cup Synthetic Proposal

Section: 271
Group Members: Meagan Maas, Iana Gueorguieva, Kurun Oberoi, Jeff Simon

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Introduction:

The informal name for the compound we are proposing to synthesize is skatole. The word skatole is derived from the Greek word skato, which means dung. This compound can be found in mammalian feces and has a sharp odor. Ironically, in low concentration, skatole has a flowery scent and is used in the manufacturing of perfumes. Another interesting fact about this molecule is that it has been found to cause pulmonary edema in goats, sheep, and several rodents, such as mice and rats.

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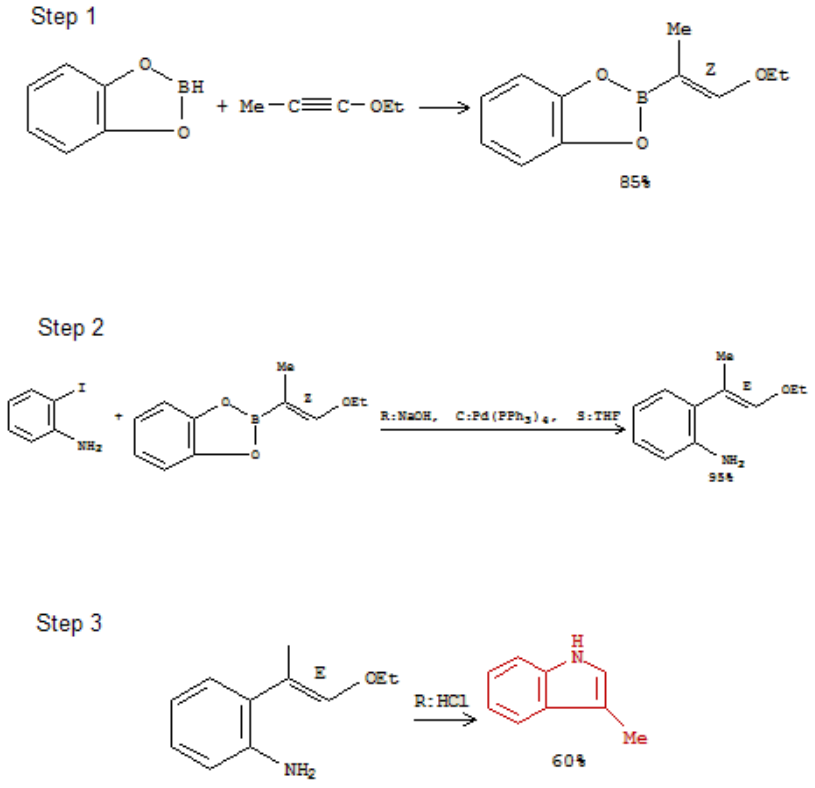
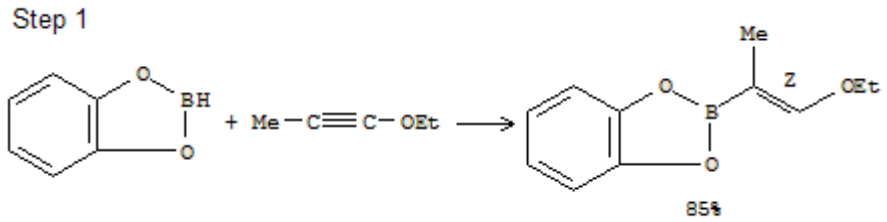
Overall synthetic reaction scheme:



Step 1

Synthetic transformation 1:



Experimental 1 Note: the scale was modified in order to produce 0.5 g of the desired product. Everything was scaled up by a factor of 35.7143.

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Expected yield: 85 % 226 g

Safety, disposal and green issues 1:

Chemical Name	Risks Associated with Each Compound
Ethyl 1-propynyl Ether (1-ethoxy-1-alkyne)	No MSDS available
1,3,2-Benzodioxiborole	Avoid contact with skin, vapor may cause eye and skin irritation, flammable, explosive in the presence of water

Safety precautions will involve working in a hood to avoid inhalation and eye irritation, using gloves to avoid skin contact, using an anhydrous environment for all reactions, and carefully handling and not ingesting any reagents. 1,3,2-Benzodioxiborole is a flammable and corrosive reagent that reacts violently with water. This compound causes burns and vapors may cause drowsiness and dizziness.[ii]

This reagent needs to be carefully disposed in a labeled organic bottle, and then cautiously handled by a professional. 1-ethoxy-1-alkyne should also be disposed in a second organic bottle (due to its high level of reactivity), and properly handled by a professional laboratory technician.[iii]

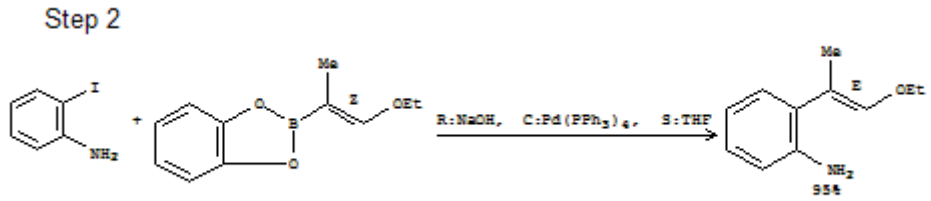
Some decomposition Products that may be hazardous to the enviornment: Carbon monoxide and Carbon dioxide.

Characterization methods for product

Boiling point analysis: This product has an experimentally determined boiling point of 90-94^{o}C.

Step 2

Synthetic transformation 2:



Experimental 2

To a 1000 ml beaker was added 1.25 g (1.07 mmol) tetrakis (triphenylphosphine) palladium, 4.286 g (107.143 mmol) powdered sodium hydroxide, and 107.143 ml tetrahydrofuran.[iv]

To this mixture was added 9.46 g (35.7413 mmol) N-amino-2-iodoaniline and 9.82 ml (42.14 mmol) 2-(1-ethoxy-1-propen-2-yl)-1,3,2-benzodioxaborole (product of step 1), and the mixture was heated under reflux for 4 h. After this time, 35.7413 ml of 3 normal (3 M) sodium hydroxide and 7.14 ml 30% hydrogen peroxide were added.

The product was extracted with 1.785 L benzene, washed with 1.071 L brine and dried with magnesium sulfate. The solvent was then evaporated and the product (2-(2-acetylaminophenyl)-1-ethoxypropene) evaluated with column chromatography using 2:1 benzene:ethyl acetate. Melting point analysis reveals that the product has melting point 73˚C. [v]*Note: The experimental section uses N-acetyl-2-iodoaniline, but the literature indicated that either compound gave the same reaction under the same conditions.*

Expected yield: 95% 5.928 g

Safety, disposal and green issues 2:

Chemical Name	Risks Associated with Each Compound
Tetrakis(triphenylphosphine)palladium	avoid contact with skin, eyes; should not be inhaled
Sodium hydroxide	causes severe burns
THF	highly flammable, may form explosive peroxides, eye/skin irritant, toxic, water sensitive
N-amino-2-iodoaniline	skin/eye irritant (for all analogs; specifics not found)
Benzodioxaborole	eye/skin irritant, flammable, not to be inhaled
Benzene	flammable, toxic, carcinogenic, eye/skin irritant, don't inhale/ingest
Hydrogen Peroxide	flammable, strong oxidizer, eye/skin irritant, don't inhale/ingest
Ethyl acetate	flammable, eye/skin irritant
2-(2-acetylaminophenyl)-1-ethoxypropene	flammable, water sensitive, skin/eye irritant

Safety precautions will involve working in a hood to avoid inhalation and eye irritation, using gloves to avoid skin contact, using an anhydrous environment for all reactions, and carefully handling and not ingesting any reagents.

The palladium reagent, THF, the dioxaborole, benzene, hydrogen peroxide, and ethyl acetate can be normally disposed of using acetone. The iodated reagent will be disposed of in halogenated waste, and sodium hydroxide will be disposed of in basic waste. [vi]

Flammable and oxidizing reagents could cause environmental concerns if they combust (carbon monoxides could be a by-product), so these reagents will be handled with great caution.

Characterization methods for product: (2-(2-acetylaminophenyl)-1-ethoxypropene)[vii]

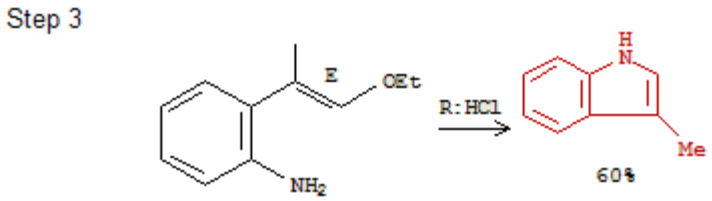
- **H-NMR ($CDCl_3$) - Delta values (ppm)[viii]**
  1.30 (t, 3H, J= 7 Hz); 1.92 (doublet, 3H, J=1.3 Hz); 3.7 (broad singlet, 2H);
  3.86 (quartet, 2H, J= 7 Hz); 6.13 (doublet, 1H, J=1.3 Hz); 6.5-7.2 (multiplet, 4H)

- **IR Spectroscopy**
  This compound has characteristic frequencies at around 1600 and 760 cm^{-1}.

- **Melting Point Analysis**
  This compound has an experimentally determined melting point of 73˚C.

Step 3

Synthetic transformation 3:



Experimental 3 Note: the scale was modified in order to produce 0.5 g of the desired product. This is a factor of 35.7143.

1.393 g (6.357 mmol) of the product of step 2 was added to 178.57 ml tetrahydrofuran. Next was added 3.57 ml 2 normal (2 M) hydrochloric acid, and this mixture was stirred for at least 16 hours.[ix]

Expected yield: 60% 0.5 g

Safety, disposal and green issues 3:

Chemical Name	Risks Associated with Each Compound
THF	highly flammable, may form explosive peroxides, eye/skin irritant, toxic, water sensitive
Hydrochloric acid	causes burns, eye irritant
2-(2-acetylaminophenyl)-1-ethoxypropene	flammable, water sensitive, skin/eye irritant
3-methylindole	skin/eye/respiratory tract irritant

Safety precautions involve working in a hood to avoid eye irritation and combustion, gloves to avoid skin contact, anhydrous reaction conditions.[x]

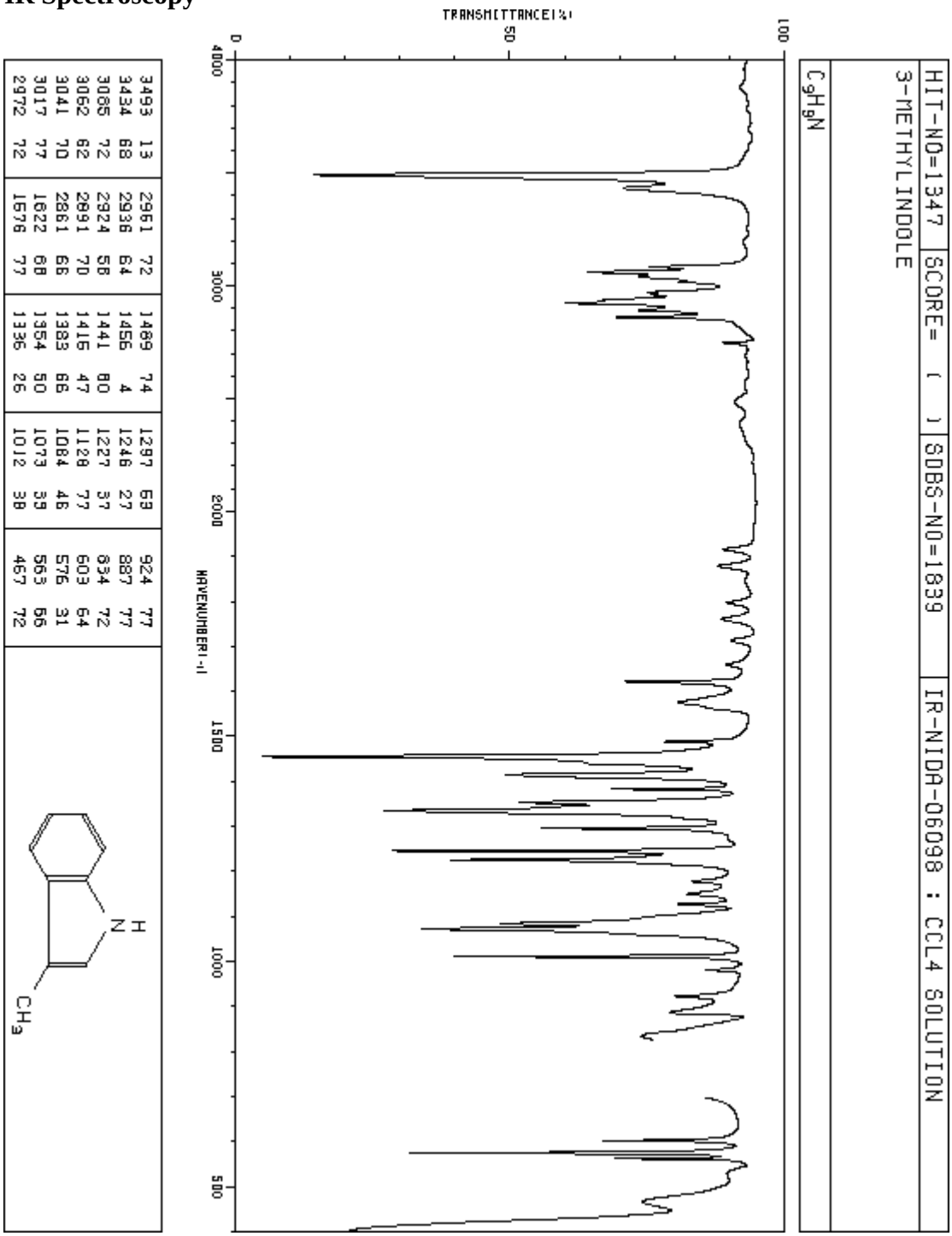
Combustible reagents could be an environmental concern, as could improper disposal of waste. Care should be taken to prevent combustion of any hydrocarbon reagents.

THF, the step 2 product, and 3-methylindole can be disposed of normally using acetone. Hydrochloric acid must be disposed of in an acid waste container.

Characterization methods for product

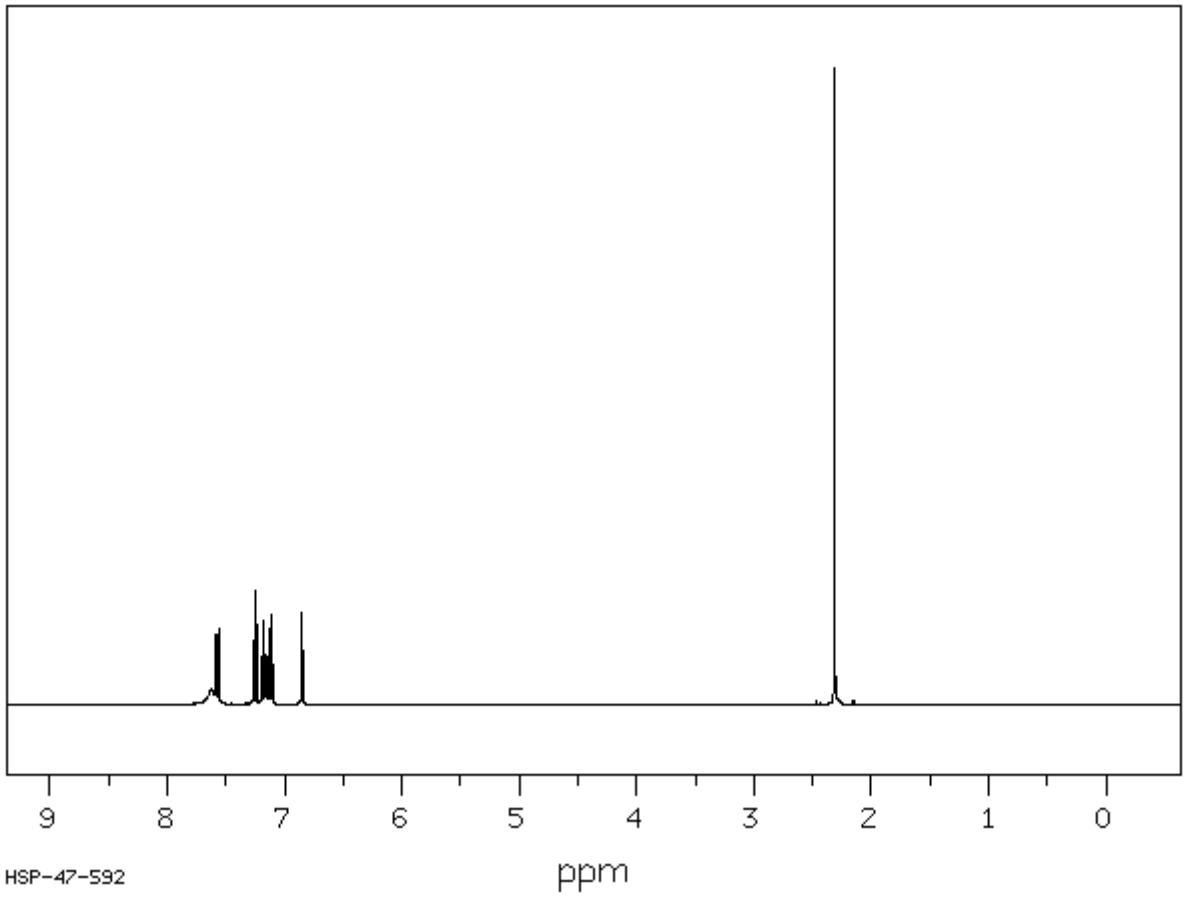
3-methylindole (skatole)

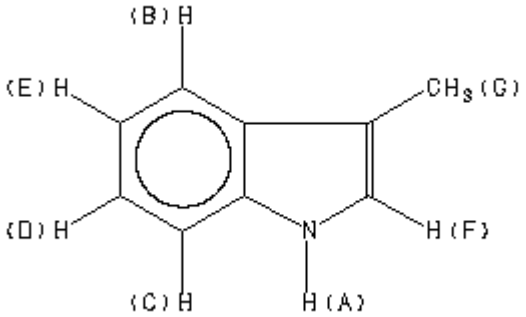
IR Spectroscopy[xi]



3493	13	2961	72	1469	74	1297	69	924	77
3434	68	2936	64	1456	4	1246	27	887	77
3085	72	2924	58	1441	80	1227	37	834	72
3062	62	2891	70	1416	47	1128	77	603	64
3041	70	2861	66	1383	66	1084	46	576	31
3017	77	1622	68	1354	50	1073	39	563	66
2972	72	1576	77	1336	26	1012	38	467	72

^{1}H NMR at 400 MHz[xii]





Assign.	Shift(ppm)
A	7.6
B	7.571
C	7.249
D	7.174
E	7.116
F	6.853
G	2.313

Overall budget:

Chemical	**Supplier**	**Cost**	**Amt. Needed**	**Total**
Benzodioxaborole	*Sigma-Aldrich Co.*	$3.35 per mL	142.86 ml	$478.58
1-ethoxy-1-alkyne	N/A	To be Synthesized (See Appendix II)	N/A	$354.478
2M HCl	*Sigma-Aldrich Co.*	$0.13 per mL	3.57 ml	$0.46
Tetrahydrofuran	*Sigma-Aldrich Co.*	$0.06 per mL	285.713 ml	$17.00
Tetrakis(triphenylphosphine) palladium	*Sigma-Aldrich Co.*	$26.00 per g	1.25 g	$32.63
3 M NaOH				
Ethyl Acetate	*Sigma-Aldrich Co.*	$0.04 per mL	40 mL	$1.56
Benzene	*Sigma-Aldrich Co.*	$0.05 per mL	1.75 L + ~ 40 mL for column chromatography	$87.60
Brine	*Sigma-Aldrich Co.*	$0.03 per mL	1.071 L	$32.13
MgSO4	*Sigma-Aldrich Co.*	$0.11 per g	3 g	$0.33
Powdered NaOH	*Sigma-Aldrich Co.*	$0.56	4.286 g	$2.40

Total costs per synthesis: $1007.17

References (include at least two different sources for your experimentals):

Step 1:
Miyaura, N.; Koji, M.; Suginome, H. *J. Org. Chem.* **1982**, *47*, 2117-2120.

Satoh, M.; Miyaura, N.; Suzuki, A. *Synthesis.* **1987,** *1987*, 373-377.

Step 2:
Satoh, M.; Miyaura, N.; Suzuki, A. *Synthesis.* **1987,** *1987*, 373-377.

Beugalmans, R.; Roussi, G. J. *Chem. Soc. Chem. Commun.* **1979**, 950.

Step 3
Kaneko, C.; Fujii, H.; Kawai, S.; Hashiba, K.; Karasawa, Y.; Wakai, M; Hayashi, R; Somei, M. *Fac. Pharm. Sci.* **1982**, *30*, 74-85.

Beugalmans, R.; Roussi, G. J. *Chem. Soc. Chem. Commun.* **1979**, 950.
Sigma Aldrich MSDS. Retrieved February 5, 2006 from the World Wide Web:

Endnotes

[i] Satoh, M.; Miyaura, N.; Suzuki, A. *Synthesis.* **1987,** *1987*, 373-377.

[ii] Sigma Aldrich MSDS. Retrieved February 5, 2006 from the World Wide Web: http://www.sigmaaldrich.com/cgi-bin/hsrun/Suite7/Suite/HAHTpage/Suite.HsSigmaAdvancedSearch.formAction

[iii] Sigma Aldrich MSDS. Retrieved February 5, 2006 from the World Wide Web: http://www.sigmaaldrich.com/cgi-bin/hsrun/Suite7/Suite/HAHTpage/Suite.HsSigmaAdvancedSearch.formAction

[iv] Beugalmans, R.; Roussi, G. J. *Chem. Soc. Chem. Commun.* **1979**, 950.

[v] Satoh, M.; Miyaura, N.; Suzuki, A. *Synthesis.* **1987,** *1987*, 373-377.

[vi] Spectral Database for Organic Compounds SDBS. Retrieved February 5, 2006 from the World Wide Web: http://www.aist.go.jp/RIODB/SDBS/cgi-bin/direct_frame_top.cgi?lang=eng

[vii] Spectral Database for Organic Compounds SDBS. Retrieved February 5, 2006 from the World Wide Web: http://www.aist.go.jp/RIODB/SDBS/cgi-bin/direct_frame_top.cgi?lang=eng

[viii] Satoh, M.; Miyaura, N.; Suzuki, A. *Synthesis.* **1987,** *1987*, 373-377.

[ix] Kaneko, C.; Fujii, H.; Kawai, S.; Hashiba, K.; Karasawa, Y.; Wakai, M; Hayashi, R; Somei, M. *Fac. Pharm. Sci.* **1982**, *30*, 74-85.

[x] Sigma Aldrich MSDS. Retrieved February 5, 2006 from the World Wide Web: http://www.sigmaaldrich.com/cgi-bin/hsrun/Suite7/Suite/HAHTpage/Suite.HsSigmaAdvancedSearch.formAction

[xi] Spectral Database for Organic Compounds SDBS. Retrieved February 5, 2006 from the World Wide Web: http://www.aist.go.jp/RIODB/SDBS/cgi-bin/direct_frame_top.cgi?lang=eng

[xii] Spectral Database for Organic Compounds SDBS. Retrieved February 5, 2006 from the World Wide Web: http://www.aist.go.jp/RIODB/SDBS/cgi-bin/direct_frame_top.cgi?lang=eng

Appendix I

Conversions and Calculations

In the experimental, the author stated that a 91% yield was equal to 0.91 mmol of product (see page 376), which implies that a 100% yield is 1 mmol. In the synthesis of the acetylated derivative (NHAc group) of our compound, the authors had a 76% yield of 0.168 grams of product. If we used the unacetylated derivative that gives our target molecule, the yield is 95% (page 375, row 1). Therefore, 95% yield implies 0.95 mmol of product.

Molecular formula of **8**: $C_{11}H_{15}NO$
0.95 mmol * (11*12 + 15*1 + 14*1 + 16*1 mg/mmol) = 166 mg **8**

The yield of our target molecule from the next step of the synthesis was 60% according to the literature (page 375). We see in the experimental section that 0.178 mmol of the product of step 2 was added, and that the yield was 99% or 0.175 mmol, which implies that 100% yield would give 0.178 mmol. (0.175 mmol/0.99 = .178 mmol as 100%) A 60% yield would give 0.6 * 0.178 = 0.1068 mmol.

Molecular formula of skatole: C_9H_9N
0.1068 mmol * (12*9 + 9*1 + 14*1 mg/mmol) = 14.0 mg skatole expected to form before scaling up.

These calculations were performed prior to our scaling up the experiment. At this point our experiement was scaled up by a factor of 35.7143.

Appendix II

One Pot Synthesis of 1-ethoxy-1-alkyne (A reagent for the synthesis of "Skatole")

A 1L three neck flask is equipped with a condenser, a stirrer, and a gas inlet tube. The flask is immersed in an acetone dry-ice bath and anhydrous ammonia (1.233 L) is introduced into the flask. The tube is replaced with a stopper. Crushed hydrated Fe $(NO_3)_3$ (1.028 g) is added to the slowly stirred ammonia. Freshly cut sodium (77.3 g, 3.35 mol) is added in chunks over a 60 minute period. After the formation of NaNH2 is complete, the stopper is replaced by a dropping funnel containing chloroacetaldehyde diethyl acetal (156.46 g, 1.028 mol) and addition is made over a period of 30 min. After 30-60 minutes, the mixture becomes light gray. A freshly distilled alkyl halide (1.54 mol) is added rapidly through the addition funnel. This is followed by the addition of pentane (246.72 mL) and additional cooled saturated NH_4Cl solution (760.72 mL). The contents of the flask are transferred to a sep funnel and the bottom aqueous layer was removed and extracted with pentane. The resulting compound is dried with $MgSO_4$ and the pentane is removed through distillation. Vacuum filtration yields the product, 1-ethoxy-1-alkyne.

Yield = 72%

Factor= *2.056

Chemical	**Supplier**	**Cost**	**Amt. Needed**	**Total**
Anhydrous Ammonia	*Sigma-Aldrich Co.*	$0.16 per mL	1.233 L	$200.36
Sodium	*Sigma-Aldrich Co.*	$0.47 per g	77.3 g	$36.47
hydrated Fe $(NO_3)_3$	*Sigma-Aldrich Co.*	$0.07 per g	1.028 g	$0.07
chloroacetaldehyde diethyl acetal	*Sigma-Aldrich Co.*	$0.25 per g	156.46 g	$39.43
pentane	*Sigma-Aldrich Co.*	$0.04 per mL	246.72 mL	$9.35
NH_4Cl	*Sigma-Aldrich Co.*	$0.09 per mL	760.72 mL	$68.46
$MgSO_4$	*Sigma-Aldrich Co.*	$0.11 per g	3 g	$0.33
				Total = $354.47

Reference: Stalick, W.M.; Hazlett, R.N., Morris, R.E.; *Synthesis*. **1988**, *1988*, 287-290.