Supporting Information

for

Total Synthesis of the *Kopsia lapidilecta* Alkaloid (±)-Lapidilectine B

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- Discussion and photocopies of variable temperature ¹H NMR spectra (25-75 °C in CDCl₃) of **50**. (S39-S47)
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General Experimental Methods: All reactions were performed under an atmosphere of dry nitrogen or argon in flame-dried glassware equipped with tightly fitted rubber septa. All syringes and needles were oven-dried and cooled in a desiccator before use. Reactions at 0 °C were carried out in an ice/water bath. Reactions at -78 °C were carried out in a dry ice/acetone bath. Solvents were freshly dried before use. Toluene, benzene, methylene chloride (CH₂Cl₂), triethyl amine, diisopropylamine, diisopropylethylamine and acetonitrile were distilled from calcium hydride. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl. Methanol, ethanol, and isopropanol were distilled from anhydrous calcium sulfate. *N*-Methylpyrrolidinone (NMP) and tetrachloroethylene were purchased anhydrous from Aldrich Chemical Company and stored over 4 Å molecular sieves. Alternatively, methylene chloride, tetrahydrofuran and diethyl ether were purified by passage through a Solvtek™ solvent purification system of anhydrous basic alumina. *n*-Butyllithium was purchased from the Lithium Corporation of America (Lithco) and Aldrich Chemical Company, and titrated with diphenylacetic acid prior to use. All reactions were monitored by analytical thin layer chromatography (TLC), which was conducted on precoated silica gel plates (Scientific Absorbents, Inc., 250 µm glass-backed hard layer, F₂₅₄ indicator). For visualization, TLC plates were either placed under ultraviolet light, or stained with iodine-silica gel, phosphomolybdic acid solution or anisaldehyde stain. Chromatography refers to flash chromatography, which was performed according to the general procedure described by Still and coworkers (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 4923) using ICN (Sili-Tech 32-60, 60 Å) silica gel purchased from Bodman Chemicals.

The chemical shifts for proton nuclear magnetic resonance spectra (¹H NMR) are reported as δ values, in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard (0.00 ppm), or relative to residual chloroform (7.26 ppm). Data are reported in the following manner: chemical shift (multiplicity, coupling constant (*J*) in hertz (Hz), integrated intensity). Multiplicities are reported using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext., sextet; m, multiplet; br, broad; app, apparent. Assignments and stereochemical determinations were made on the basis of two-dimensional correlated off-resonance spectroscopy (COSY) experiments as well as one and two-dimensional nuclear Overhauser effect spectroscopy (NOESY). Chemical shifts in the ¹³C NMR spectra are reported as δ values in ppm relative to CDCl₃ as an internal standard (77.00 ppm).

STANDARD PROTON PARAMETERS

Pulse Sequence: s2p1
 Solvent: CDCl₃
 Ambient temperature
 INOVA-500 "Sn.Chem. LSA.UMich.Edu"
 PULSE SEQUENCE
 Relax. delay: 1.000 sec
 Pulse: 39.9 degrees
 Acq. time: 2.500 sec
 Width: 8000.0 Hz
 16 repetitions
 OBSERVE: H1, 499.9042705 MHz
 DATA PROCESSING
 FI size: 65536
 Total time: 3 min, 44 sec

21

¹H NMR
 (CDCl₃)
 500 MHz

19

¹H NMR
(CDCl₃)
400 MHz

S4

DATE	2-14-57
5F	367 424
57	79 0
54	5933 000
51	2768
1D	2768
1D	5600
52/01	000 305
FM	7 0
FD	0 0
A0	277
N2	512
N5	70
1E	207
FM	0300
FD	0
02	00L Pd
1B	0 0
5B	0 0
2X	40 00
57	0 0
F1	5 5200
H2/34	0 0340
FM/54	77 402
FM/54	75
33/4	215

¹H NMR
(CDCl₃)
300 MHz

MY19034
DATE 3-11-97

ST 360 134
SF 79 0
D1 39800 000
D2 32468
D3 32468
D4 35000 000
H2/H1 505

PM 7 0
F9 0 0
A8 3 277
H6 2049
N5 41
TE 297

FM 6300
DP 63L P0

LB 0 0
GB 0 0
CX 40 00
CY 0 0
F1 8 3600
F2/CN 7 4230
PPM/CN 7 4230
5P 39800 000

25

¹H NMR
(CDCl₃)
300 MHz

STANDARD 1H OBSERVE

Solvent: CDCl₃
 Temp. 25.0 C / 298.1 K
 INOVA-400 "Zr"
 PULSE SEQUENCE
 Relax. delay arrayed
 1st pulse arrayed
 2nd pulse 40.0 degrees
 Acq. time 2.507 sec
 Width 6000.2 Hz
 Arrayed repetitions
 OBSERVE H1 399.9649499 MHz
 DATA PROCESSING
 F1 size 32768
 Total time 1 minute

27

¹H NMR
 (CDCl₃)
 400 MHz

STANDARD 1H OBSERVE

Solvent: CDCl₃
 Temp: 25.0 C / 298.1 K
 INOVA-400 "Zr"
 PULSE SEQUENCE
 Relax. delay arrayed
 1st pulse arrayed
 2nd pulse 40.0 degrees
 Acq. time 2.507 sec
 Width 6000.2 Hz
 Arrayed repetitions
 OBSERVE H1, 399.3649646 MHz
 DATA PROCESSING
 F1 size 32768
 Total time 1 minute

28

¹H NMR
 (CDCl₃)
 400 MHz

STANDARD 1H OBSERVE

Solvent: CDCl₃
 Temp: 23.0 C / 296.1 K
 INOVA-400 "Zr"
 PULSE SEQUENCE
 Relax. delay arrayed
 1st pulse arrayed
 2nd pulse 40.0 degrees
 Acq. time 2.507 sec
 Width 6000.2 Hz
 Arrayed repetitions
 OBSERVE H1, 399.9649484 MHz
 DATA PROCESSING
 FT size 32768
 Total time 1 minute

29

¹H NMR
 (CDCl₃)
 400 MHz

S9

STANDARD 1H OBSERVE

Solvent: CDCl₃
 Temp: 25.0 C / 298.1 K
 INOVA-400 "Zr"
 PULSE SEQUENCE
 Relax. delay arrayed
 1st pulse arrayed
 2nd pulse 40.0 degrees
 Acq. time 2.507 sec
 Width 6000.2 Hz
 Arrayed Repetitions
 OBSERVE H1, 399.9649488 MHz
 DATA PROCESSING
 F1 size 32768
 Total time 1 minute

30

¹H NMR
 (CDCl₃)
 400 MHz

STANDARD 1H OBSERVE

Solvent: CDCl₃
 Ambient temperature
 INOVA-400 "Zr."
 PULSE SEQUENCE
 Relax. delay arrayed
 1st pulse arrayed
 2nd pulse 30.0 degrees
 Acq. time 2.507 sec
 Width 6000.2 Hz
 Arrayed repetitions
 OBSERVE H1, 399.9649473 MHz
 DATA PROCESSING
 FT size 32768
 Total time 3 minutes

31

¹H NMR
 (CDCl₃)
 400 MHz

STANDARD 1H OBSERVE

Pulse Sequence: s2pul1
Solvent: CDCl3
Ambient temperature
File: MY024
INOVA-500 "N1.Chem.LSA.UMich.Edu"
PULSE SEQUENCE
Pulse 40.0 degrees
Acq. time 2.507 sec
Width 6000.2 Hz
Single scan
OBSERVE H1, 399.969484 MHz
DATA PROCESSING
F1 size 32768
Total time 0 min, 2 sec

32

¹H NMR
(CDCl₃)
400 MHz

STANDARD 1H OBSERVE

Solvent: CDCl₃
 Temp. 23.0 C / 296.1 K
 File: MYV0269good
 INOVA-400 "Zr"
 PULSE SEQUENCE
 Relax. delay arrayed
 1st pulse arrayed
 2nd pulse 40.0 degrees
 Acq. time 2.507 sec
 Width 6000.2 Hz
 Arrayed repetitions
 OBSERVE H1, 399.9649492 MHz
 DATA PROCESSING
 FT size 32768
 Total time 4 minutes

33

¹H NMR
 (CDCl₃)
 400 MHz

BMS
DATE 13-11-97
SF 360.134
Q1 3800.000
Q2 32788
Q3 5000.000
HZ/PT .305
PM 7.0
RD 0.0
AQ 3.277
RG 4096
NS 124
TE 297
FW 6300
Q2 0.0
DP 63L P0
LB 0.0
GB 0.0
CX 40.00
CY 0.0
F1 8.500P
F2 77.099P
PMA/CM 77.243
SR 3983.59

34

¹H NMR
(CDCl₃)
300 MHz

S14

STANDARD 1H OBSERVE

Solvent: CDCl₃
 Temp: 25.0 C / 298.1 K
 INOVA-400 "Zr"
 PULSE SEQUENCE
 Relax. delay arrayed
 1st pulse arrayed
 2nd pulse 30.4 degrees
 Acq. time 2.507 sec
 Width 6000.2 Hz
 Arrayed repetitions
 OBSERVE H1 399.9649488 MHz
 DATA PROCESSING
 FT size 32768
 Total time 2 minutes

35

¹H NMR
 (CDCl₃)
 400 MHz

STANDARD 1H OBSERVE

Solvent: CDCl₃
 Temp: 25.0 C / 298.1 K
 File: MYIY064
 INOVA-500 "N1.Chem.LSA.UMich.Edu"
 PULSE SEQUENCE
 Relax. delay arrayed
 1st pulse arrayed
 2nd pulse 30.4 degrees
 Acq. time 2.507 sec
 Width 6000.2 Hz
 Arrayed repetitions
 OBSERVE H1: 399.3649495 MHz
 DATA PROCESSING
 FT size 32768
 Total time 4 minutes

36

¹H NMR
 (CDCl₃)
 400 MHz

STANDARD 1H OBSERVE

Solvent: CDCl₃
 Ambient temperature
 INOVA-400 "Zirconium.Chem.LSA.Umich.Edu"
 PULSE SEQUENCE
 Relax. delay arrayed
 1st pulse arrayed
 2nd pulse arrayed
 Acq. time 2.507 sec
 Width 6000.2 Hz
 Arrayed repetitions
 OBSERVE H1, 399.9649646 MHz
 DATA PROCESSING
 FT size 32768
 Total time 1 minute

14

¹H NMR
 (CDCl₃)
 400 MHz

STANDARD 1H OBSERVE

Solvent: CDCl₃
Ambient temperature
INOVA-400 "Zircontium.Chem.LSA.UNIcn.Edu"
PULSE SEQUENCE: gcosy
Relax. delay arrayed
Acq. time 0.132 sec
Width 3889.2 Hz
2D Width 3889.2 Hz
Arrayed repetitions
256 increments
OBSERVE H1 399.9643646 MHz
DATA PROCESSING
Sine del 0.066 sec
F1 DATA PROCESSING
Sine del 0.033 sec
F1 size 1024 x 1024
Total time 19 minutes

14

¹H-¹H COSY NMR
(CDCl₃)
400 MHz

STANDARD 1H OBSERVE

exp1 std1h

SAMPLE	2 98	DEC. & VI	399.967
date	Nov	dfreq	30
solvent	CDCl3	dn	0
file	exp	dpwr	0
ACQUISITION	399.967	dot	0
sfrq	399.967	dm	0
in	H1	dmf	0
at	2.507	dres	8855
np	30080	1.0	
sw	6000.2	homo	
fb	3000	PROCESSIONG	
bs	16	wtfile	ft
tpwr	57	proc	not used
pw	8.4	fn	
dl	0	math	
tof	0	Werr	
nt	1000	Wexp	
ct	272	Wbs	
atock	not used	Wnt	
gain	not used		
FLAGS	n		
11	n		
in	y		
dp	nm		
hs	nm		
DISPLAY			
SP	-91.6		
WD	3677.1		
VS	195		
SC	0		
WC	250		
hZmm	14.71		
is	790.18		
rfl	984.1		
rffp	0		
th	55		
ins	2.000		
nm	cdc		
ph

37

¹H NMR
(CDCl₃)
400 MHz

STANDARD 1H OBSERVE

Solvent: CDCl3
 Temp. 25.0 C / 298.1 K
 File: MYV030
 INOVA-400 "Zr"
 PULSE SEQUENCE
 Relax. delay arrayed
 1st pulse arrayed
 2nd pulse 39.3 degrees
 Acq. time 2.507 sec
 Width 6000.2 Hz
 Arrayed repetitions
 OBSERVE H1 389.9649484 MHz
 DATA PROCESSING
 FT size 32768
 Total time 4 minutes

38

¹H NMR
 (CDCl₃)
 400 MHz

S20

STANDARD 1H OBSERVE

Solvent: CDCl3
 Temp: 23.0 C / 296.1 K
 Mercury-300 "z" inc. chem. isa. umtch. edu"
 PULSE SEQUENCE
 Relax. delay arrayed
 1st pulse arrayed
 2nd pulse 40.0 degrees
 Acq. time 1.998 sec
 Width 4500.5 Hz
 Arrayed repetitions
 OBSERVE H1, 300.0732294 MHz
 DATA PROCESSING
 FT size 32768
 Total time 3 minutes

39
¹H NMR
 (CDCl₃)
 300 MHz

STANDARD 1H OBSERVE

Solvent: CDCl3
 Temp: 25.0 C / 298.1 K
 File: MY1V082a "Zinc.chem.jsa.umich.edu"
 Mercury-300
 PULSE SEQUENCE
 Relax. delay arrayed
 1st pulse arrayed
 2nd pulse 45.8 degrees
 Acq. time 1.998 sec
 Width 4500.5 Hz
 Arrayed repetitions
 OBSERVE H1, 300.0732288 MHz
 DATA PROCESSING
 F1 size 32768
 Total time 1 minute

40

¹H NMR
 (CDCl₃)
 300 MHz

STANDARD 1H OBSERVE

Solvent: CDCl₃
 Temp. 25.0 C / 298.1 K
 Mercury-300 "zinc.chem.1sa.umich.edu"
 PULSE SEQUENCE
 Relax. delay arrayed
 1st pulse arrayed
 2nd pulse 45.0 degrees
 Acq. time 1.998 sec
 Width 4500.5 Hz
 Arrayed repetitions
 OBSERVE H1, 300.0732321 MHz
 DATA PROCESSING
 FT size 32768
 Total time 3 minutes

41

¹H NMR
 (CDCl₃)
 300 MHz

STANDARD 1H OBSERVE

Solvent: CDCl₃
 Temp. 25.0 C / 298.1 K
 INOVA-400 "Zr"
 PULSE SEQUENCE
 Relax. delay arrayed
 1st pulse arrayed
 2nd pulse 30.4 degrees
 Acq. time 2.507 sec
 Width 6000.2 Hz
 Arrayed repetitions
 OBSERVE H1 399.9649493 MHz
 DATA PROCESSING
 FT size 32768
 Total time 1 minute

42

¹H NMR
 (CDCl₃)
 400 MHz

STANDARD 1H OBSERVE

Solvent: CDCl₃
Temp: 20.0 C / 293.1 K
File: MYIV094
INOVA-100 "Zirconium.Chem.LSA.UMich.Edu"
PULSE SEQUENCE
Relax: delay arrayed
1st pulse arrayed
2nd pulse arrayed
Acq: time 2.507 sec
Width 6000.2 Hz
Arrayed repetitions
OBSERVE H1: 399.9649497 MHz
DATA PROCESSING
F1 size 32768
Total time 1 minute

43

¹H NMR
(CDCl₃)
400 MHz

distilled DCM

Pulse Sequence: s2pu1

Solvent: CDCl3

Ambient temperature

File: ps1234aH

INOVA-500 "C1"

PULSE SEQUENCE

Pulse 40.0 degrees

Acq. time 2.666 sec

Width 6000.6 Hz

1024 repetitions

08SERVE H1 399.9649487 MHz

DATA PROCESSING

FT size 32768

Total time 45 min, 39 sec

48

¹H NMR
(CDCl₃)
400 MHz

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pu1

Solvent: CDCl₃

Ambient temperature

File: ps208301

INOVA-500 "N1" Chem ISA 101inch Four"

PULSE SEQUENCE:

Relax. delay 1.000 sec

Pulse 38.9 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

32 repetitions

OBSERVE H1, 409.9042610 MHz

DATA PROCESSING

FT size 65536

Total time 29 min, 14 sec

49

¹H NMR
(CDCl₃)
500 MHz

S27

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: ps1241ch
INOVA-500 "Cu"
PULSE SEQUENCE
Pulse: 40.0 degrees
Acq. time: 2.666 sec
Width: 6000.6 Hz
104 repetitions
OBSERVE H1, 399.3649487 MHz
DATA PROCESSING
F1 size 32768
Total time 11 min, 24 sec

50

¹H NMR
(CDCl₃)
400 MHz

S28

STANDARD 1H OBSERVE

Pulse Sequence: szpul
Solvent: CDCl3
Ambient temperature
INOVA-400 "Zr"
PULSE SEQUENCE
Pulse 40.0 degrees
Acq. time 2.666 sec
Width 6000.6 Hz
256 repetitions
OBSERVE H1, 399.9649487 MHz
DATA PROCESSING
Ft size 32768
Total time 11 min, 24 sec

52

¹H NMR
(CDCl₃)
400 MHz

STANDARD PROTON PARAMETERS

Pulse Sequence: s2pul

Solvent: CDCl₃

Ambient temperature

File: ps2156bh

INOVA-500 "N1.Chem.LSA.UMich.Edu"

PULSE SEQUENCE

Relax. delay 1.000 sec

Pulse 40.4 degrees

Acq. time 2.500 sec

Width 8000.0 Hz

76 repetitions

OBSERVE H1, 499.9042610 MHz

DATA PROCESSING

FT size 65536

Total time 14 min, 58 sec

53

¹H NMR
(CDCl₃)
500 MHz

S30

STANDARD 1H OBSERVE

Pulse Sequence: s2pul

Solvent: CDCl3

Ambient Temperature

File: ps12384h

INOVA-500 "Cq"

PULSE SEQUENCE

Pulse 40.0 degrees

Acq. time 2.666 sec

Width 6000.6 Hz

256 repetitions

OBSERVE H1, 399.9649487 MHz

DATA PROCESSING

FI size 32768

Total time 11 min, 24 sec

54

¹H NMR
(CDCl₃)
400 MHz

S31

STANDARD 1H OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
File: ps1269ah
INOVA-500 "Cu"
PULSE SEQUENCE
Pulse 40.0 degrees
Acq. time 2.666 sec
Width 8000.0 Hz
256 repetitions
OBSERVE H1, 399.9649483 MHz
DATA PROCESSING
F1 size 65536
Total time 11 min, 24 sec

55

¹H NMR
(CDCl₃)
400 MHz

STANDARD 1H OBSERVE

Pulse Sequence: s2pu1
Solvent: CDCl3
Ambient temperature
File: ps2169h
INOVA-500 "Cu"
PULSE SEQUENCE
Pulse 45.0 degrees
Acq. time 2.666 sec
Width 6000.6 Hz
55 repetitions
OBSERVE H1 399.964901 MHz
DATA PROCESSING
FT size 32768
Total time 11 min, 24 sec

56

¹H NMR
(CDCl₃)
400 MHz

S33

~~BXUB~~ R

DATE 25-10-95
 SF 300.133
 SI 0.000
 ST 4900.000
 TD 32768
 SM 4000.000
 HZ/PT .244
 PM 6.0
 RD 0.0
 AG 4.096
 RG 40
 NS 6
 TE 297
 FM 5000
 D2 0.0
 DP 63L P0
 LB 0.0
 GB 0.0
 CX 40.00
 CY 0.0
 F1 0.0
 F2 2.100P
 HZ/CM 60.779
 PPV/CM .203
 SR 3364.51

9

¹H NMR
 (CDCl₃)
 300 MHz

S34

BMS
DATE 3-11-95

SF 300 133
SY 0 0
Q1 4900.000
S1 33758
F0 33768
SM 4000 000
HZ/P1 244
PM 5.0
PD 1.0
A1 4.095
MS 2.0
TE 297
FM 50.0
Q2 0.0
CP 63L P1
LR 0.0
2B 0.0
CX 40.00
F1 0.0
F2/CW 75.781
PRM/CW .252
SR 3351.18

10

¹H NMR
(CDCl₃)
300 MHz

BRUKER

DATE 16-7-96

SF 300.133
 SY 0.0
 O1 4900.000
 S1 32768
 TD 32768
 SW 4000.000
 HZ/PT .244
 PM 6.0
 RD 0.0
 AD 4.006
 NS 21
 TC 297
 FM 5000
 O2 0.0
 DP 6.3L P0
 LR 0.0
 SO 0.0
 CY 40.00
 F1 9.001P
 F2 -.099P
 HZ/CM 68.280
 PPM/CM .227
 SR 3367.82

¹H NMR
 (CDCl₃)
 300 MHz

STANDARD 1H OBSERVE

Solvent: CDCl3
Temp: 25.0 C / 298.1 K
Mercury-300 "zinc.chem.1sa.umich.edu"
PULSE SEQUENCE
Relax. delay arrayed
1st pulse arrayed
2nd pulse 40.1 degrees
Acq. time 1.398 sec
Width 4500.5 Hz
Arrayed repetitions
OBSERVE H1, 300.0732283 MHz
DATA PROCESSING
FT size 32768
Total time 1 minute

59

¹H NMR
(CDCl₃)
300 MHz

STANDARD 1H OBSERVE

Solvent: CDCl3
Ambient temperature
Mercury-300 "zinc.chem.1sa.umich.edu"
PULSE SEQUENCE
Relax. delay arrayed
1st pulse arrayed
2nd pulse 40.0 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
Arrayed repetitions
OBSERVE H1, 300.0732296 MHz
DATA PROCESSING
F1 size 32768
Total time 1 minute

60

¹H NMR
(CDCl₃)
300 MHz

S38

Variable ^1H NMR Spectra of **50**

In order to confirm that **50** was a single diastereomer exhibiting carbamate rotamers, as opposed to an inseparable mixture of diastereomers, we undertook a series of variable temperature ^1H NMR experiments. A solution of **50** in CDCl_3 was degassed by three freeze-pump-thaw cycles in an NMR tube, which was sealed under vacuum while the solution was frozen with a dry ice-acetone bath ($-78\text{ }^\circ\text{C}$). The spectra of the evacuated NMR sample was taken at $5\text{ }^\circ\text{C}$ intervals from $25\text{ }^\circ\text{C}$ to $75\text{ }^\circ\text{C}$, reshimming the spectrometer after each interval.

The spectra on the following pages show that proton $\text{H}(\text{b})$ is near its coalescence point at $25\text{ }^\circ\text{C}$ in CDCl_3 due to restricted rotation around the methyl carbamate C-N bond. Proton $\text{H}(\text{b})$ reaches its fast-exchange limit and forms a broad singlet by $50\text{ }^\circ\text{C}$. Proton $\text{H}(\text{b})$ also appears to be deshielded to 6.8 ppm anisotropically by the proximate methyl carbamate group. Neighboring proton $\text{H}(\text{c})$ at $25\text{ }^\circ\text{C}$ seems unaffected by the methyl carbamate group, but is split into a $2 : 1$ ratio of rotamers from the closer Teoc carbamate. Proton $\text{H}(\text{c})$ reaches the slow-exchange limit at about $55\text{ }^\circ\text{C}$ and approaches the fast-exchange limit at $75\text{ }^\circ\text{C}$, forming a broad singlet. Proton $\text{H}(\text{d})$, which is a $2 : 1$ ratio of rotamers at $25\text{ }^\circ\text{C}$, reaches its slow-exchange limit at about $50\text{ }^\circ\text{C}$ and reaches fast-exchange by $65\text{ }^\circ\text{C}$, sharpening into a singlet. It is clear therefore that **50** is a single diastereomer, a supposition supported by TLC and HPLC analysis which both show only one spot or peak under a variety of conditions. Protons $\text{H}(\text{b})$ - $\text{H}(\text{d})$ were assigned by ^1H - ^1H COSY NMR (not shown).

Pulse Sequence: s2pul

Solvent: CDCl3

Ambient temperature

File: hawkt25

INOVA-500 "H1"

PULSE SEQUENCE

Pulse 35.0 degrees

Acq. time 2.666 sec

Width 6000.6 Hz

32 repetitions

OBSERVE H1, 399.9649645 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 32768

Total time 11 min, 24 sec

50

VT ¹H NMR
(CDCl₃, 400 MHz)
25 °C

S40

Pulse Sequence: s2pu1

Solvent: CDCl3

Ambient temperature

File: hawk125

INOVA-500 "N1"

PULSE SEQUENCE

Pulse 35.0 degrees

Acq. time 2.666 sec

Width 6000.6 Hz

32 repetitions

OBSERVE H1, 399.9649645 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 32768

Total time 11 min, 24 sec

50

H_a

S41

VT ¹H NMR
(CDCl₃, 400 MHz)
25 °C

H_d

H_c

H_b

7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 ppm

Pulse Sequence: s2pul

Solvent: CDCl₃
 Temp: 45.0 C / 318.1 K
 File: hawk145
 INOVA-500 "N1"

PULSE SEQUENCE

Pulse 35.0 degrees
 Acq. time 2.666 sec
 Width 6000.6 Hz
 16 repetitions

OBSERVE H1, 399.9649487 MHz

DATA PROCESSING

Line broadening 0.2 Hz
 FT size 32768
 Total time 0 min, 42 sec

50

VT-1H NMR
 (CDCl₃, 400 MHz)
 45 °C

S42

Pulse Sequence: s2pul

Solvent: CDCl₃

Temp: 45.0 C / 318.1 K

File: hawkT45

INNOVA-500 "N1"

PULSE SEQUENCE

Pulse 35.0 degrees

Acq. time 2.666 sec

Width 6000.6 Hz

16 repetitions

OBSERVE H1 399.9648487 MHz

DATA PROCESSING

Line broadening 0.2 Hz

FT size 32768

Total time 0 min, 42 sec

50

H_a

H_d

S43

VT ¹H NMR
(CDCl₃, 400 MHz)
45 °C

H_b

H_c

Pulse Sequence: s2pul
 Solvent: CDCl₃
 Temp: 60.0 C / 333.1 K
 File: hawkT60
 INOVA-500 "N1"
 PULSE SEQUENCE
 Pulse 35.0 degrees
 Acq. time 2.666 sec
 Width 6000.6 Hz
 16 repetitions
 OBSERVE H1 399.9649534 MHz
 DATA PROCESSING
 Line broadening 0.2 Hz
 FI size 32766
 Total time 0 min, 42 sec

50

VT ¹H NMR
 (CDCl₃, 400 MHz)
 60 °C

S44

Pulse Sequence: s2pu1

Solvent: CDCl₃
Temp. 60.0 C / 333.1 K
File: haw0160
INNOVA-500 "N"
PULSE SEQUENCE
Pulse 35.00 degrees
Acq. time 2.586 sec
Width 6000.6 Hz
16 repetitions
OBSERVE H1, 399.964955
DATA PROCESSING
Line broadening 0.2 Hz
FI scale 32768
Total time 0 min, 42 sec

05

S45

VT ^1H NMR
(CDCl_3 , 400 MHz)
60 °C

Pulse Sequence: s2pul
 Solvent: CDCl₃
 Temp: 75.0 C / 348.1 K
 File: hawk175
 INOVA-500 "N1"
 PULSE SEQUENCE
 Pulse 35.0 degrees
 Acq. time 2.686 sec
 Width 6000.6 Hz
 16 repetitions
 OBSERVE H1, 399.9649534 MHz
 DATA PROCESSING
 Line broadening 0.2 Hz
 FT size 32768
 Total time 0 min, 42 sec

50

VT ¹H NMR
 (CDCl₃, 400 MHz)
 75 °C

Pulse Sequence: s2pul
 Solvent: CDCl₃
 Temp: 75.0 C / 348.1 K
 File: hawk175
 INOVA-500 "N1"
 PULSE SEQUENCE
 Pulse 35.0 degrees
 Acq. time 2.666 sec
 Width 6000.6 Hz
 16 repetitions
 OBSERVE H1, 399.9649534 MHz
 DATA PROCESSING
 Line broadening 0.2 Hz
 FT size 32768
 Total time 0 min, 42 sec

50

VT ¹H NMR
 (CDCl₃, 400 MHz)
 75 °C

H_a

H_b

H_c

H_d

7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 ppm

S47

DATE	08-11-95
CLASS	601
SE	204.132
AF	RJ 337.600
G1	337.600
TD	327.600
ID	327.600
HZ/PT	.153
PK	5 C
PN	4 U
PQ	13
US	297
FM	322.5
PP	5
GP	6UL Pu
LR	1 U
SR	1 U
CX	40 G
FY	8 .1 P
F1	8 .1 P
HZ/M	40 52.2
BPM/V	3.75
SN	203.75

58

S48

Synthesis of Aminocarbonylation Precursors **10** and **11**

Novel compounds **10** and **11** were synthesized for model studies of the aminocarbonylation reaction outlined in Scheme 2. The commercially available 1,4-cyclohexanedione *mono*-ethylene ketal **57** was converted into the known alkenyl triflate **58**¹⁶ by sequential treatment with LDA and *N*-phenyltriflamide at $-78\text{ }^{\circ}\text{C}$; a method similar to one recently reported by Carreño and coworkers.¹⁶ The alkenyl triflate **58** was converted into alkenyl stannane **9** using the procedure of Wulff and coworkers.¹⁷ The desired enone **10** was formed through the carbonylative Stille coupling^{18,19} of known iodoaniline **8** (Wender, P. A.; White, A. W. *Tetrahedron* **1983**, *39*, 3767-3776) and alkenyl stannane **9**. Luche reduction (Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *100*, 2226-2227) of enone **10** provided allylic alcohol **11** in 61% yield along with the undesired cyclic carbamate **59** in 39% yield.

8-(Trifluoromethanesulfonyl)oxy-1,4-dioxaspiro[4.5]dec-7-ene (58). This known¹⁶ compound has recently been synthesized by Carreño and coworkers by a method similar to the one described here.¹⁶ A solution of LDA was prepared from diisopropylamine (0.61 g, 6.1 mmol) and *n*-butyllithium (2.90 mL of a 2.1 M solution in hexane, 6.1 mmol) in THF (18 mL) at -10 °C. After 10 min, it was cooled to -78 °C and a solution of 1,4-cyclohexanedione *mono*-ethylene ketal **57** (0.866 g, 5.54 mmol) in THF (10 mL) was added in a dropwise fashion. After 2 h at -78 °C, *N*-phenyltrifluoromethanesulfonimide (1.97 g, 5.54 mmol) was added in one portion. The reaction was allowed to warm to 0 °C over 4 h. The reaction mixture was diluted with 20% ethyl acetate/hexane, washed with water (2x), brine (1x), dried (MgSO₄) and concentrated. Chromatography (10% ethyl acetate/hexanes) afforded 1.23 g (77%) of the title compound as a light yellow oil. *R*_f = 0.26 (15% ethyl acetate/hexanes); IR (CHCl₃) 1691 (m), 1417 (s), 1375 (s), 1247 (s), 1142 (s) cm⁻¹; ¹H and ¹³C NMR data matched that of Carreño and coworkers.¹⁶

8-Trimethylstannyl-1,4-dioxaspiro[4.5]dec-7-ene (9). Hexamethylditin (1.55 g, 4.74 mmol), tetrakis(triphenylphosphine)palladium (0.55 g, 0.47 mmol) and anhydrous lithium chloride (1.28 g, 30.2 mmol, flame-dried in air, cooled *in vacuo*) were added to a solution of the alkenyl triflate **58** (1.38 g, 4.77 mmol) in THF (47 mL) at rt and then heated to reflux. After 2 h, the reaction was cooled to rt, diluted with hexane, washed with water (3x), brine (1x), dried (MgSO₄) and concentrated. Chromatography (7% ethyl acetate/hexanes) gave 0.91 g (63%) of the title compound as a colorless oil. *R*_f = 0.23 (10% ethyl acetate/hexanes); IR (neat) 1614 (m), 1430 (m), 1113 (s) cm⁻¹; ¹H NMR (300

MHz, CDCl₃) δ 5.78-5.72 (m, 1 H), 3.99 (s, 4 H), 2.46-2.30 (m, 4 H), 1.75 (t, J = 6.1 Hz, 2 H), 0.12 (s, 9 H); ¹³C NMR (75 MHz, CDCl₃) δ 133.0, 107.5, 64.5, 38.0, 32.0, 30.5, -10.0; MS (EI, 70 eV) m/z (rel int) 304 (M⁺, 17), 289 ([M – Me]⁺, 85), 245 (100), 165 (Me₃Sn⁺, 64); HRMS (EI, 70 eV) calcd for C₁₁H₂₀O₂Sn (M⁺) 304.0485, found 304.0497.

8-[2-(Methoxycarbonylamino)benzoyl]-1,4-dioxaspiro[4.5]dec-7-ene (10). Anhydrous lithium chloride (0.420 g, 9.91 mmol, flame-dried in air, cooled *in vacuo*), tris(dibenzylideneacetone)-dipalladium(0)•chloroform adduct (0.061 g, 0.059 mmol), triphenylarsine (0.157 g, 0.510 mmol), alkenyl stannane **9** (0.705 g, 2.33 mmol), aryl iodide **8** (0.658 g, 2.37 mmol; see Wender, P. A.; White, A. W. *Tetrahedron* **1983**, *39*, 3767-3776) and anhydrous NMP (20 mL) were added to a Fischer-Porter pressure vessel. The vessel was purged and pressurized with carbon monoxide (70 psi) and immersed in a 75 °C oil bath. After 12 h the vessel was cooled and vented. The mixture was diluted with ether, washed with water (3x) and brine (1x), then dried (MgSO₄) and concentrated. Chromatography (30% ethyl acetate/hexanes) gave 549 mg (74%) of the title compound as a yellow oil. R_f = 0.20 (20% ethyl acetate/hexanes); IR (CHCl₃) 3411 (m), 1732 (s), 1628 (s), 1583 (s), 1510 (s), 1450 (s), 1061 (s) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 9.56 (s, 1 H), 8.25 (d, J = 8.0 Hz, 1 H), 7.60-7.40 (m, 2 H), 7.03 (t, J = 6.0 Hz, 1 H), 6.35-6.25 (m, 1 H), 4.02 (s, 4 H), 3.75 (s, 3 H), 2.80-2.35 (m, 4 H), 1.88 (t, J = 6.0 Hz, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 198.5, 154.0, 139.4, 139.0, 138.2, 133.0, 131.8, 122.2, 120.4, 107.0, 64.8, 52.2, 36.3, 30.8, 24.0; MS (EI, 70 eV) m/z (rel int) 317 (M⁺, 1), 289 (53), 257 (6), 203 (19), 188 (18), 144 (100), 86 (59); HRMS (EI, 70 eV) calcd for C₁₇H₁₉NO₅ (M⁺) 317.1263, found 317.1270.

8-(1,4-Dioxaspiro[4.5]dec-7-enyl) 2-(methoxycarbonylamino)phenyl methanol (11)
and 4-(8-(1,4-dioxaspiro[4.5]dec-7-enyl)-1,4-dihydrobenzo[d][1,3]oxazin-2-one (59).

Cerium(III) chloride heptahydrate (0.12 g, 0.32 mmol) was added to a solution of enone **10** (0.10 g, 0.32 mmol) in MeOH (2.5 mL) at rt. After 2 h, sodium borohydride (0.061 g, 1.6 mmol) was added in a portionwise fashion. The resulting suspension was stirred for an additional 5 h at rt. The reaction was quenched with 3.7% aqueous HCl and extracted with ether (3x). The combined organic layers were separated, dried (MgSO₄) and concentrated. Chromatography (60% to 80% ether/hexanes gradient) gave 52 mg (61%) of **11**, 30 mg (39%) of **59**, along with 15 mg of the recovered enone **10**. The yield was based on the recovered starting material.

11: R_f = 0.20 (40% ethyl acetate/hexanes); IR (CHCl₃) 3412 (s), 1732 (s), 1584 (s), 1518 (s), 1450 (s), 1115 (s), 1061 (s) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.05 (d, J = 7.7 Hz, 1 H), 7.30-7.20 (m, 1 H), 7.10-6.95 (m, 3 H), 5.65-5.56 (m, 1 H), 4.04 (s, 4 H), 3.75 (s, 3 H), 2.50-2.35 (m, 4 H), 1.95-1.86 (m, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 153.9, 135.5, 134.6, 132.6, 128.0, 127.7, 125.6, 122.8, 119.0, 107.5, 64.5, 64.4, 52.1, 35.9, 31.4, 29.6, 25.0; MS (EI, 70 eV) m/z (rel int) 319 (M⁺, 27), 301 (31), 287 (13), 269 (29), 215 (28), 198 (42), 156 (51), 86 (100); HRMS (EI, 70 eV) calcd for C₁₇H₂₁NO₅ (M⁺) 319.1420, found 319.1412.

59: R_f = 0.21 (60:30:10 hexanes/ethyl acetate/MeOH); IR (CHCl₃) 3430 (m), 1712 (s), 1602 (s), 1497 (s) cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.70 (s, 1 H), 7.30-7.20 (m, 1 H), 7.08-7.02 (m, 2 H), 6.85 (d, J = 8.0 Hz, 1 H), 5.79 (s, 1 H), 5.70-5.62 (m, 1 H), 3.98 (s, 4 H), 2.44-2.20 (m, 4 H), 1.80 (t, J = 6.0 Hz, 2 H); ¹³C NMR (90 MHz, CDCl₃) δ 152.9, 135.4, 133.9, 129.2, 126.1, 125.4, 123.3, 119.3, 114.2, 107.6, 83.2, 64.4, 35.7,

30.7, 22.9; MS (CI, NH₃) *m/z* (rel int) 288 ([M + H]⁺, 100), 287 (M⁺, 28), 258 (17), 244 (84), 214 (18), 200 (49), 182 (20), 144 (34); HRMS (CI, NH₃) calcd for C₁₆H₁₈NO₄ ([M + H]⁺) 288.1236, found 288.1235.

Conversion of 29 into 30

It was found that undesired cyclized carbamate **29** (formed in Scheme 7) could be recycled into the useful intermediate **31** in moderate yield through a sequence of carbamate methanolysis with sodium methoxide, *bis*-TMS ether formation and methyl carbamate reinstallation.

a) 1) NaOMe, MeOH, 2) TMS-imidazole, 100 °C (51%);
b) 1) *t*-BuLi, THF, -30 °C, 2) ClCO₂Me (38%).

(1'*R,3'*S**,4'*R**)-1,2-Dihydroindol-3-one-2-spiro-4'-[1'-benzyloxy-3'-(1,2-bis(trimethylsilyloxy)ethyl)cyclohexane] (60).** Sodium methoxide (66 mg, 1.2 mmol) was added to a solution of cyclic carbamate **29** (48 mg, 0.12 mmol) in methanol (2 mL) at rt. After 2 h, the reaction was filtered through a pad of silica and concentrated. Without purification, the crude was treated with 1-(trimethylsilyl)imidazole (2 mL) and the mixture was heated at 100 °C. After 1.5 h, it was cooled to rt, diluted with hexane and washed with water (2x). The combined aqueous layers were extracted with hexane (1x) and the combined organic solution was dried (MgSO₄) and concentrated. Chromatography (15% to 20% ethyl acetate/hexanes) gave 32 mg (51% overall) of **60** as a yellow solid (m.p. 137-140 °C); *R_f* = 0.25 (20% ethyl acetate/hexanes); IR (CHCl₃) 3420 (w), 1697 (s), 1618 (s) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.60 (app d, *J* = 7.7 Hz,

1 H), 7.43-7.21 (m, 6 H), 6.87-6.78 (m, 2 H), 5.08 (s, 1 H), 4.52 (ABq, $\Delta\nu = 18.9$ Hz, $J_{AB} = 12.4$ Hz, 2 H), 3.84-3.78 (m, 1 H), 3.50-3.40 (m, 2 H), 3.22-3.12 (m, 1 H), 2.70-2.60 (m, 1 H), 2.20-1.76 (m, 3 H), 1.60-1.40 (m, 1 H), 1.22-1.12 (m, 1 H), -0.07 (s, 9 H), -0.11 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3) δ 204.6, 160.4, 138.9, 136.3, 128.3, 127.4, 125.0, 122.4, 119.3, 113.5, 75.6, 71.4, 69.7, 68.8, 65.5, 39.3, 31.0, 29.2, 26.7, 0.3, -0.7; MS (CI, NH_3) m/z (rel int) 512 ($[\text{M} + \text{H}]^+$, 100), 440 (7), 241 (9), 19 (16), 192 (54), 108 (6), 91 (3); HRMS (CI, NH_3) $\text{C}_{28}\text{H}_{42}\text{NO}_4\text{Si}_2$ ($[\text{M} + \text{H}]^+$) calcd 512.2652, found 512.2654.

Compound **31** was then prepared from **60** in the following manner: *tert*-butyllithium (0.036 mL of a 1.7 M solution in pentane, 0.062 mmol) was added to a solution of **60** (32 mg, 0.062 mmol) in THF (1 mL) at -30 °C. After 15 min methyl chloroformate (29 mg, 0.30 mmol) was added at -30 °C. The resulting mixture was allowed to warm to rt over a 30 min period, then diluted with ether, washed with water (1x), dried (MgSO_4) and concentrated. Chromatography (10% ethyl acetate/hexanes) afforded 13 mg (38%) of **31** as a light yellow oil.