Synthesis of Cortistatin Alkaloids and a Versatile Synthesis of Isoquinolines

Thesis Advisor: Professor Andrew G. Myers Chong Si

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Abstract

The cortistatins are a recently identified class of marine natural products that were found to exhibit potent and selective inhibition of human umbilical vein endothelial cells (HUVECs), making them promising leads for the development of anti-angiogenic drugs. In our synthesis, we envisioned that natural cortistatins and unnatural analogs could be prepared by late-stage introduction of isoquinolines to 17-keto precursors, and that these differentially substituted precursors could all be derived from a common key intermediate **112**.

We developed a robust synthetic route to prepare gram quantities of key intermediate **112** starting from readily available benzylzinc reagent **116** and enol triflate **117**. Key intermediate **112** was next converted to cortistatin precursors **108**, **109**, **110**, and **111** in three to eight steps, representing each of the four natural cortistatin ABC-ring substitution patterns. Subsequently, a generally applicable method was developed to introduce the isoquinoline moiety. After complexation to *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), 7-lithio-isoquinoline added to 17-keto precursors to provide the corresponding 1,2-addition products; the resulting tertiary alcohols underwent radical deoxygenation via their trifluoroacetates to afford the desired (17*S*)-products. This organolithium-addition-deoxygenation sequence provided cortistatins A (**1**, on a 20-mg scale), J (**9**), K (**10**), and L (**11**) in good overall yields. We also synthesized

cortistatin primary amines (**176** and **186**) and used them to prepare several cortistatin based affinity reagents. By employing these reagents in pull-down experiments, we identified a 55-kD membrane kinase as a putative protein target of cortistatins.

We wanted to prepare cortistatin analogs with isoquinoline modifications due to the importance of this ring for the biological activity of cortistatins. This led us to develop a novel and versatile synthesis of substituted isoquinolines. In our method, lithiated *o*-tolualdehyde *tert*-butylimines were condensed with different nitriles to generate eneamido anion intermediates, which were trapped *in situ* with various electrophiles at the C4-position, affording a wide range of substituted isoquinolines. Further diversification was achieved by modification of the work-up conditions and by subsequent transformations.

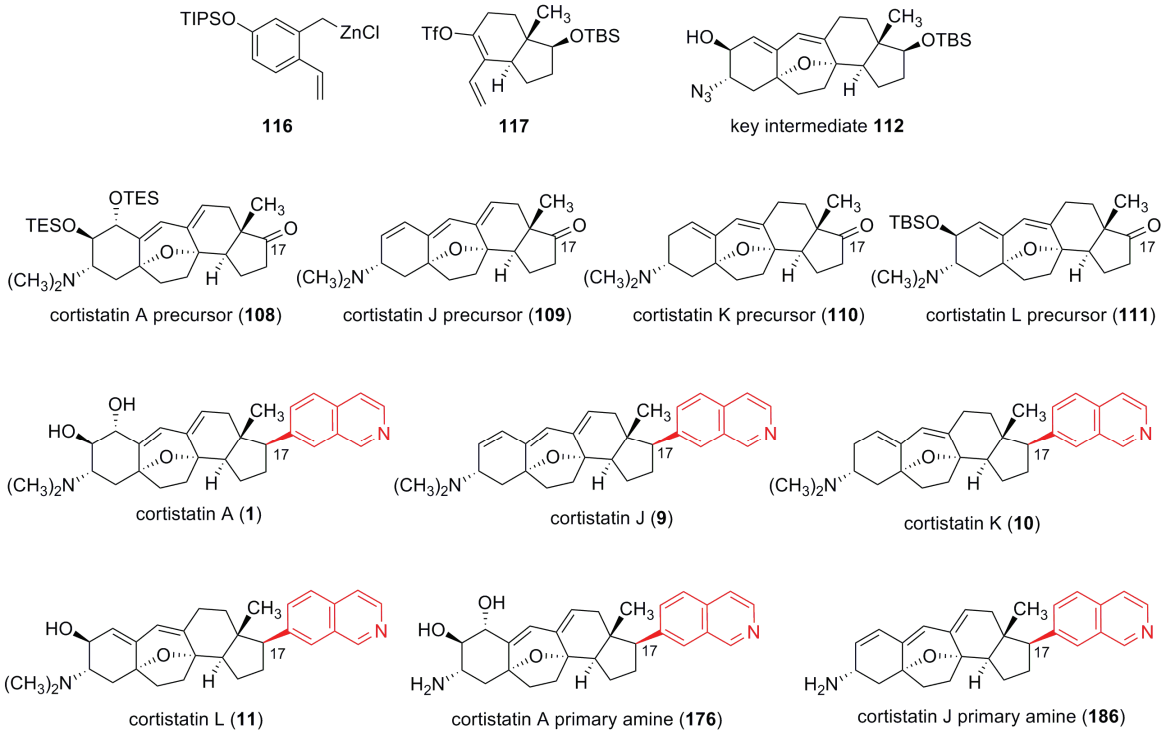

Table of Contents

Acknowledgements

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List of Abbreviations

AIBN	azobisisobutyronitrile
Burgess reagent	methyl *N*-(triethylammoniumsulphonyl)carbamate
BzCl	benzoyl chloride
c	concentration (g/100 mL)
CAM	aqueous ceric ammonium molybdate solution
CI	chemical ionization
cis	*L.*, on the same side
COSY	correlation spectroscopy
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMF	*N,N*-dimethylformamide
DMP	Dess–Martin periodinane
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
E	*Ger.*, entgegen
ED_{50}	50% effective dose
ee	enantiomeric excess
EI	electron impact

ent	enantiomer
equiv	equivalent
ESI	electrospray ionization
Et_3N	triethylamine
EtOH	ethanol
FTIR	Fourier transform infrared
g	gram
GI_{50}	50% growth inhibition
hν	light
HFIPA	1,1,1,3,3,3-hexafluoro-2-propanol
HMBC	heteronuclear multiple bond correlation
HPLC	high-pressure liquid chromatography
HRMS	high-resolution mass spectrometry
HSQC	heteronuclear single quantum coherence
Hz	hertz
IBX	*o*-iodoxybenzoic acid
J	coupling constant
K562	human chronic myelogenous leukemia cells
KB3-1	KB epidermoid carcinoma cells
KHMDS	potassium hexamethyldisilazide
$KMnO_4$	aqueous potassium permanganate solution
K-selectride	potassium tri-*sec*-butylborohydride
LRMS	low-resolution mass spectrometry

M	molar
m-CPBA	*meta*-chloroperoxybenzoic acid
MEMCl	methoxyethoxymethyl chloride
mg	milligram
MHz	megahertz
mL	milliliter
m/z	mass to charge ratio
μL	microliter
mmol	millimole
μmol	micromole
MOM	methoxymethyl
MPO	4-methoxypyridine *N*-oxide
MsCl	methanesulfonyl chloride
NaHMDS	sodium hexamethyldisilazide
NBS	*N*-bromosuccinimide
Neuro2A	murine neuroblastoma cells
NHDF	normal human dermal fibroblasts
NOE	nuclear Overhauser effect
NMR	nuclear magnetic resonance
p-anisaldehyde	acidic ethanolic *p*-anisaldehyde solution
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate

psi	pounds per square inch
p-TsOH	*p*-toluenesulfonic acid
Py	pyridine
R	rectus (Cahn–Ingold–Prelog system)
R_f	retention factor
rt	room temperature
S	sinister (Cahn–Ingold–Prelog system)
S-Phos	2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl
TASF	tris(dimethylamino)sulfonium difluorotrimethylsilicate
TBAA	tetra-*n*-butylammonium acetate
TBAF	tetra-*n*-butylammonium fluoride
TBCHD	2,4,4,6-tetrabromo-2,5-cyclohexadienone
TBSCl	*tert*-butyldimethylsilyl chloride
TBSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
TESCl	chlorotriethylsilane
TESOTf	triethylsilyl trifluoromethanesulfonate
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TIPSOTf	triisopropylsilyl trifluoromethanesulfonate
TLC	thin-layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMSCl	chlorotrimethylsilane

TMSOTf	trimethylsilyl trifluoromethanesulfonate
TPAP	tetrapropylammonium perruthenate
trans	*L.*, across
Z	*Ger.*, zusammen

Chapter 1

Introduction to the Cortistatin Family of Natural Products

Isolation and Biological Activities of the Cortistatins

The cortistatins are a family of eleven steroidal alkaloids isolated from the marine sponge *Corticium simplex* by the Kobayashi group in 2006 and 2007 (Figure 1.1).[1] Structurally, there are four types of substitution patterns in the ABC-ring part among all the cortistatins, as in cortistatin A (**1**), B (**2**), C (**3**), and D (**4**); cortistatin E (**5**), G (**7**), H (**8**), and K (**10**); cortistatin F (**6**), and J (**9**); and cortistatin L (**11**). They all share the same 9(10→19)-*abeo*-androstane core structure[2] with an unusual C5,C8 oxa-bridge and a C3 dimethylamino group, but are different in the degree and position of oxygenation and unsaturation along the northern edge of ABC-ring. In the D-ring part, most cortistatins have a unique isoquinoline substituent attached at C17 position, while cortistatin E (**5**), F (**6**), G (**7**), and H (**8**) have an *N*,3-dimethylpiperidine or 3-methylpyridine ring in their C17 side chains.

More significantly, several of cortistatins exhibit strong inhibition against the proliferation of human umbilical vein endothelial cells (HUVECs), but are much less potent against a panel of other cancerous and normal human cell lines (Table 1.1).[1,3] The HUVECs are isolated from normal human umbilical vein, and are a standard model to study angiogenesis.[4] Angiogenesis is the growth of new capillary blood vessels from pre-

[1] (a) Aoki, S.; Watanabe, Y.; Sanagawa, M.; Setiawan, A.; Kotoku, N.; Kobayashi, M. *J. Am. Chem. Soc.* **2006**, *128*, 3148–3149. (b) Watanabe, Y.; Aoki, S.; Tanabe, D.; Setiawan, A.; Kobayashi, M. *Tetrahedron* **2007**, *63*, 4074–4079. (c) Aoki, S.; Watanabe, Y.; Tanabe, D.; Setiawan, A.; Arai, M.; Kobayashi, M. *Tetrahedron Lett.* **2007**, *48*, 4485–4488.

[2] In the 9(10→19)-*abeo*-androstane structure, the C19 angular methyl group of a typical steroid framework (androstane) is incorporated into the B-ring to form a seven-membered ring.

[3] The authors showed that cortistan A also inhibites the migration and tubular formation of HUVECs: Aoki, S.; Watanabe, Y.; Tanabe, D.; Arai, M.; Suna, H.; Miyamoto, K.; Tsujibo, H.; Tsujikawa, K.; Yamamoto, H.; Kobayashi, M. *Bioorg. Med. Chem.* **2007**, *15*, 6758–6762.

[4] Rhim, J. S.; Tsai, W.; Chen, Z.; Chen, Z.; Van Waes, C.; Burger, A. M.; Lautenberger, J. A. *Carcinogenesis* **1998**, *19*, 673–681.

Figure 1.1 The Cortistatin Family of Natural Products.

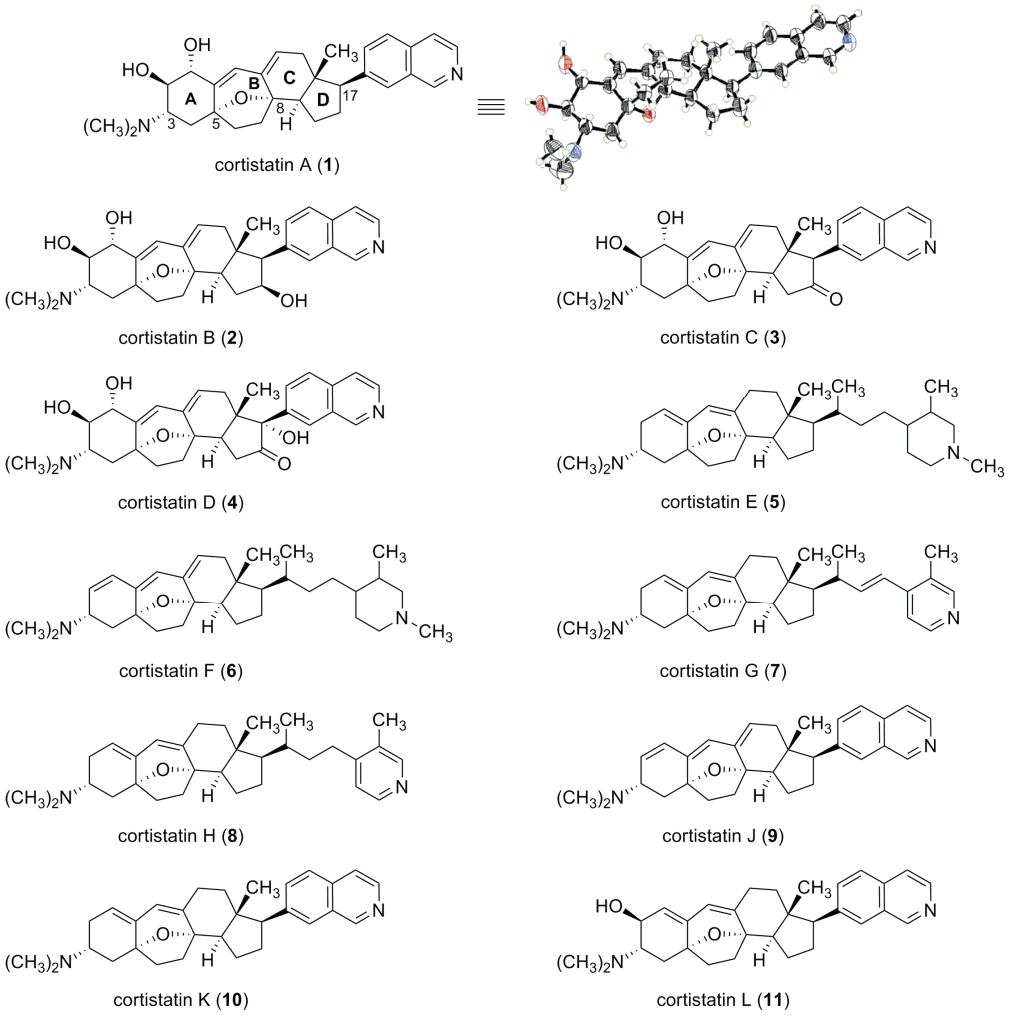

Table 1.1 Growth Inhibitions of Cortistatins against HUVECs and other Cell Lines.

Cell Line	GI_{50} (μM)			
	Cortistatin A (**1**)	Cortistatin J (**9**)	Cortistatin K (**10**)	Cortistatin L(**11**)
HUVECs	0.0018	0.008	0.04	0.023
KB3-1	7.0	9.1	10.2	14
Neuro2A	6.0	3.3	3.0	2.8
K562	7.0	3.3	3.9	4.3
NHDF	6.0	2.4	2.5	2.4

existing ones. Physiological angiogenesis could occur during reproduction, development, or wound healing, and is strictly controlled by a host of angiogenic factors; while pathological angiogenesis can be unregulated and persistent,[5] and is responsible for a wide range of diseases, including many types of cancers, autoimmune disease, age-related macular degeneration, and atherosclerosis.[6]

In 1971, Judah Folkman, a young surgeon at that time, first hypothesized that angiogenesis is necessary for the growth and metathesis of tumor cells,[7] and identified the first angiogenesis promoting factor named tumor angiogenesis factor (TAF).[8] Nine years later, the same laboratory isolated the first angiogenesis inhibitor, interferon-α/β.[9] Following the pioneering work of the Folkman group, more than 30 additional angiogenic factors, and over 400 endogenous and synthetic angiogenesis inhibitors have been discovered over the past three decades.[10] Noteworthily, the Folkman group identified several steroids (e.g. medroxyprogesterone, cortisone, and dexamethasone) that inhibit angiogenesis *in vivo* in the presence of heparin or a heparin fragment with an unknown mechanism.[11] In the mid-1990s, a couple of anti-angiogenic drugs started to enter clinical trials. In 2004, Bevacizumab, an antibody that neutralizes vascular endothelial growth factor (VEGF), was approved by the Food and Drug Administration (FDA) to treat colorectal cancer, which is the first drug developed solely as an

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[5] Hanahan, D.; Weinberg, R. A. *Cell* **2000**, *100*, 57–70.
[6] Folkman, J. *Nat. Rev. Drug Discovery* **2007**, *6*, 273–286.
[7] Folkman, J. *N. Engl. J. Med.* **1971**, *285*, 1182–1186.
[8] Folkman, J.; Merler, E.; Abernathy, C.; Williams, G. *J. Exp. Med.* **1971**, *133*, 275–288.
[9] Langer, R.; Conn, H.; Vacanti, J.; Haudenschild, C.; Folkman, J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 4331–4335.
[10] Cao, Y.; Arbiser, J.; D'Amato, R. J.; D'Amato, P. A.; Ingber, D. E.; Kerbel, R.; Klagsbrun, M.; Lim, S.; Moses, M. A.; Zetter, B.; Dvorak, H.; Langer, R. *Sci. Transl. Med.* **2011**, *3*, 114rv3.
[11] (a) Crum, R.; Szabo, S.; Folkman, J.; *Science* **1985**, *230*, 1375–1378; (b) Gross, J.; Azizkhan, R. G.; Biswas, C.; Bruns, R. R.; Hsieh, D. S.; Folkman, J. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 1176–1180.

angiogenesis inhibitor.[12,13] A number of small molecule entities, including Sorafenib (Bayer and Onyx, approved in 2005),[14] Sunitinib (Pfizer, approved in 2006),[15] Pazopanib (GlaxoSmithKline, approved in 2009),[16] and Vandetanib (AstraZeneca, approved in 2011),[17] have been developed as tyrosine kinase inhibitors (TKIs) of vascular endothelial growth factor receptors (VEGFRs) and other related receptor tyrosine kinases to treat different types of cancers (Figure 1.2). Anti-angiogenic drugs have also been approved to treat diseases other than cancer: Ranibizumab, a fragment of Bevacizumab,[18] and Pegaptanib, an anti-VEGF aptamer,[19] were both approved for the treatment of age-related macular degeneration (AMD). In addition, several drugs that were previously approved for unrelated purposes, like Thalidomide,[20] Bortezomib,[21] and

[12] Hurwitz, H.; Fehrenbacher, L.; Novotny, W.; Cartwright, T.; Hainsworth, J.; Heim, W.; Berlin, J.; Baron, A.; Griffing, S.; Holmgren, E.; Ferrara, N.; Fyfe, G.; Rogers, B.; Ross, R.; Kabbinavar, F. *N. Engl. J. Med.* **2004**, *350,* 2335–2342.

[13] Bevacizumab has since also been approved for the treatment of certain lung cancers, renal cancers, and glioblastoma multiforme of the brain; but its approval for the treatment of breast cancer was revoked in 2011; its major side effects include high blood pressure and bleeding.

[14] Wilhelm, S. M.; Carter, C.; Tang, L.; Wilkie, D.; McNabola, A.; Rong, H.; Chen, C.; Zhang, X.; Vincent,P.; McHugh, M.; Cao,Y.; Shujath,J.; Gawlak,S.; Eveleigh, D.; Rowley,B.; Liu, L.; Adnane,L.; Lynch, M.; Auclair, D.; Taylor, I.; Gedrich,R.; Voznesensky, A.; Riedl, B.; Post, L. E.; Bollag, G.; Trail, P. A. *Cancer. Res.* **2004**, *64*, 7099–7109.

[15] Roskoski, R. Jr. *Biochem. Biophys. Res. Commun.* **2007**, 356, 323–328.

[16] Sleijfer, S.; Ray-Coquard, I.; Papai. Z.; Le Cesne, A.; Scurr, M.; Schöffski, P.; Collin, F.; Pandite, L.; Marreaud, S.; De Brauwer, A.; van Glabbeke, M.; Verweij, J.; Blay, J. Y. *J. Clin. Oncol.* **2009**, *27*, 3126–3132.

[17] Herbst, R. S.; Heymach, J. V.; O'Reilly, M. S.; Onn, A.; Ryan, A. J. *Expert Opin. Investig. Drugs* **2007**, *16*, 239–249.

[18] Ranieri, G.; Patruno, R.; Ruggieri, E.; Montemurro, S.; Valerio, P.; Ribatti, D. *Curr. Med. Chem.* **2006**, *13*, 1845–1857.

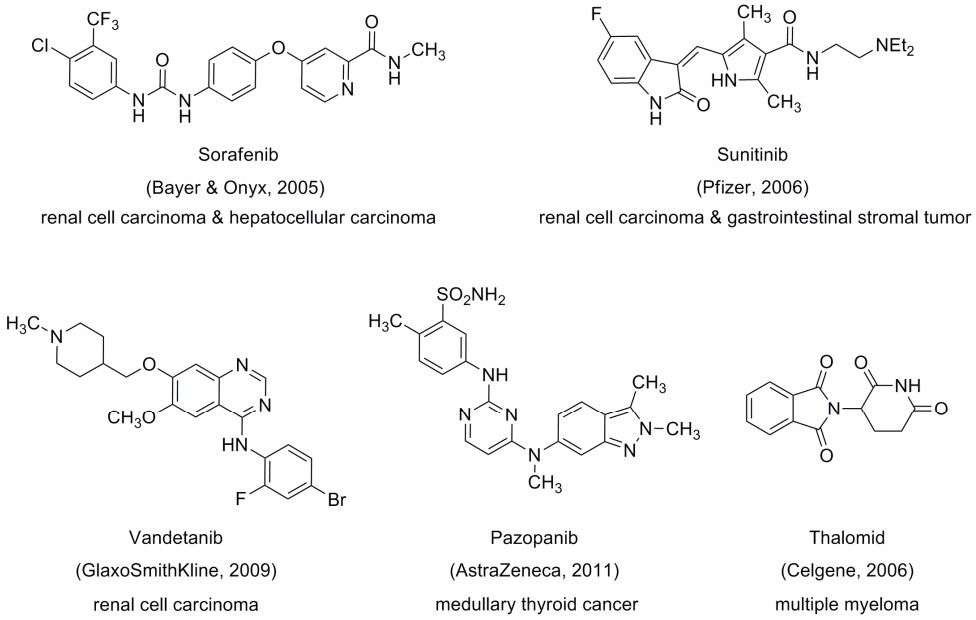
[19] Ng, E. W. M.; Shima, D. T.; Calias, R.; Cunningham, E. T. Jr.; Guyer D. R.; Adamis, A. P. *Nat. Rev. Drug Discovery* **2006**, *5*, 123–132.

[20] Thalidomide was used to treat morning sickness in the late 1950s but was later withdrawn as it caused severe birth defects; in 2006, thalidomide was approved by the FDA to treat multiple myeloma in combination with dexamethasone: Weber, D.; Rankin, K.; Gavino, M.; Delasalle, K.; Alexanian, R. *J. Clin. Oncol.* **2003**, *21*, 16–19.

[21] Bortezomib was initially approved as a protease inhibitor but later identified to have potent antiangiogenic activity: Yasui, H.; Hideshima, T.; Richardson, P. G.; Anderson, K. C. *Curr. Pharm. Biotechnol*. **2006**, *7*, 381–393.

Celecoxib,[22] were found to also have potent anti-angiogenic effects. To date, no fewer than 14 anti-angiogenic-related drugs have been approved in the United States, along with more than 30 anti-angiogenic drug candidates in clinical trials.[23]

Figure 1.2 Selected FDA Approved Small Molecule Entities with Anti-angiogenic Effect.



The potent and selective inhibition of cortistatins against HUVECs made them promising lead compounds for anti-angiogenic therapeutics; yet the molecular mechanism of cortistatins of inhibiting angiogenesis remains unclear to date. Kobayashi and co-workers observed an unidentified 110 kDa protein whose phosphorylation was inhibited by the treatment of cortistatin A.[3] In collaboration with Amgen, the Nicolaou−Chen group used an activity-based kinase profiling assay and screened 359

[22] Celecoxib was developed as a cyclooxygenase-2 enzyme (COX-2) inhibitor and also identified to possess anti-angiogenic properties: Greene, A. K.; Alwayn, I. P.; Nose, V. *Ann. Surg*. **2005**, *242*, 140–146.
[23] Li, W. W.; Li, V. W.; Hutnik, M.; Chiou, A. S. *J. Oncology* **2012**, Article ID 879623, 1−23.

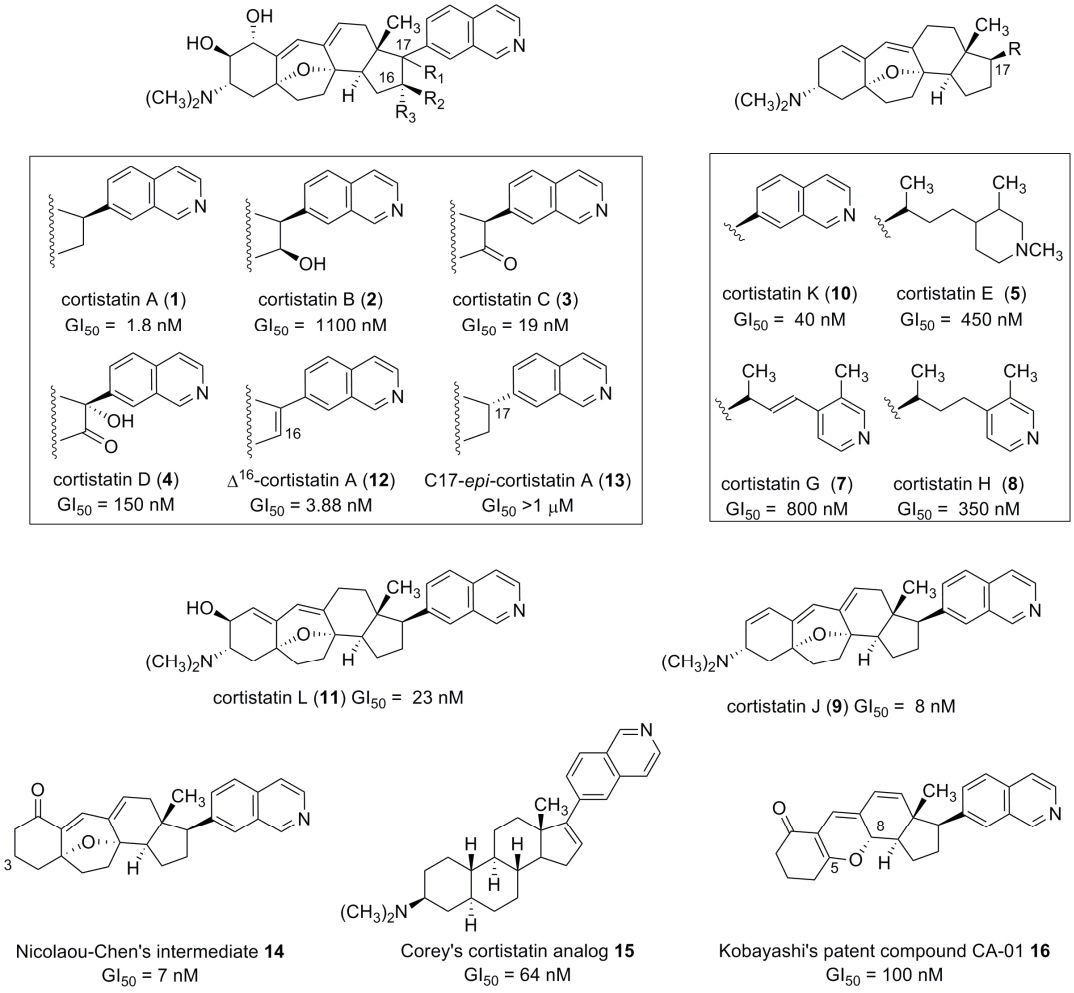
kinases *in vitro*.[24] The top four putative targets identified in the study were ROCK I, ROCK II, CDK8, and CDK 11, with CDK8 and CDK11 having binding constants (K_d values of 10 nM and 17 nM respectively) in the same range of the IC_{50} of cortstatin A in HUVECs. They further conducted homology modeling and suggested that cortistatin A might bind to the kinase hinge region through its isoquinoline substituent, with its polar A-ring exposing to solvent.

The hypothesis that the isoquinoline ring is essential for the cortistatin activity, while the ABC-ring part could tolerate certain degrees of modifications is consistent with the preliminary structure-activity relationship (SAR) data obtained from natural cortistatins as well as several synthetic cortistatin analogs (Figure 1.3). The Kobayashi group found that with different oxidation states at C16 and C17, cortistatin B (**2**), C (**3**), and D (**4**) exhibited different degrees of reduced activities in comparison with cortistatin A (**1**); and cortistatin E (**5**), G (**7**), and H (**8**), which share the same ABC-ring substitution pattern as cortistatin K (**10**) but do not possess the C17 isoquinoline substituent, lost most of their activities; in contrast, cortistatin A (**1**), J (**9**), K (**10**), and L (**11**), which contain the same D-ring pattern but are different in the ABC ring functionality, had similar low nano-molar activities against HUVECs.[1,3] The Baran group reported that Δ^{16}-cortistatin A (**12**) is almost as active as cortistatin A (**1**), while C17-*epi*-cortistatin A (**13**), with an inverse stereochemistry at C17 isoquinoline moiety, is 500-fold less active.[25] In addition, a late-stage synthetic intermediate **14** reported by the Nicolaou–Chen group, which lacks the C3 dimethylamino group and A-ring hydroxyl groups but has the C17 isoquinoline

[24] Cee, V. J.; Chen, D. Y. K.; Lee, M. R.; Nicolaou, K. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 8952–8957.
[25] Shi, J.; Shigehisa, H.; Guerrero, C. A.; Shenvi, R. A.; Li, C. C.; Baran, P. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 4328–4331.

substituent installed, retained the potency of cortistatins;[26] an estrone-derived cortistatin analog **15** synthesized by the Corey group,[27] and a simplified cortistatin analog **16** prepared in the Kobayashi group,[28] both lacking the oxabicyclo[3.2.1]octene core structure but keeping the isoquinoline appendage, also exhibited good GI_{50} values against HUVECs.

Figure 1.3 GI_{50} Values against HUVECs of Selected Natural Cortistatins and Synthetic Cortistatin Analogs.



[26] Nicolaou, K. C.; Peng, X. S.; Sun, Y. P.; Polet, D.; Zou, B.; Lim, C. S.; Chen, D. Y. K. *J. Am. Chem. Soc.* **2009**, *131*, 10587–10597.
[27] Czakó, B.; Kürti, L.; Mammoto, A.; Ingber, D. E.; Corey, E. J. *J. Am. Chem. Soc.* **2009**, *131*, 9014–9019.
[28] Kobayashi, M.; Kotoku, N. patent no.: WO/2012/036287.

Synthetic Approaches towards the Cortistatins

The remarkable biological profile, the unique molecular architecture, and the scarce of cortistatins (as the isolation chemists were also pursuing a total synthesis of cortistatins, see below) have attracted enormous efforts towards the synthesis of this class of natural products during the past few years. To date, five research groups (including our own laboratory) have accomplished the synthesis of cortistatin A, and four have finished synthesizing cortistatin J. In addition, at least two formal syntheses of cortistatins have been reported, along with numerous synthetic studies towards the cortistatin pentacyclic core structure.[29,30]

In early 2008, the Baran group form Scripps reported the first synthesis of cortistatin A starting from prednisone (**17**) (Scheme 1.1).[31,32] This inexpensive steroid was first converted to amide **18** in a six-step sequence. Subsequent Mukaiyama hydration was followed by a couple protection group manipulations to afford orthoamide **19**. The C19 angular methyl group was then selectively bis-brominated by an *in situ* generated acetoxy hypobromite (AcOBr) from bromine and bisacetoxyiodobenzene, and the C2 free alcohol was protected, providing β-keto dibromide **20**. Treating this bromide with 1,8-

[29] For two reviews, see: (a) Nising, C. F.; Brase, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 9389–9391; (b) Chen, D. Y.-K.; Tseng, C.-C.; *Org. Biomol. Chem.* **2010**, *8*, 2900–2911.

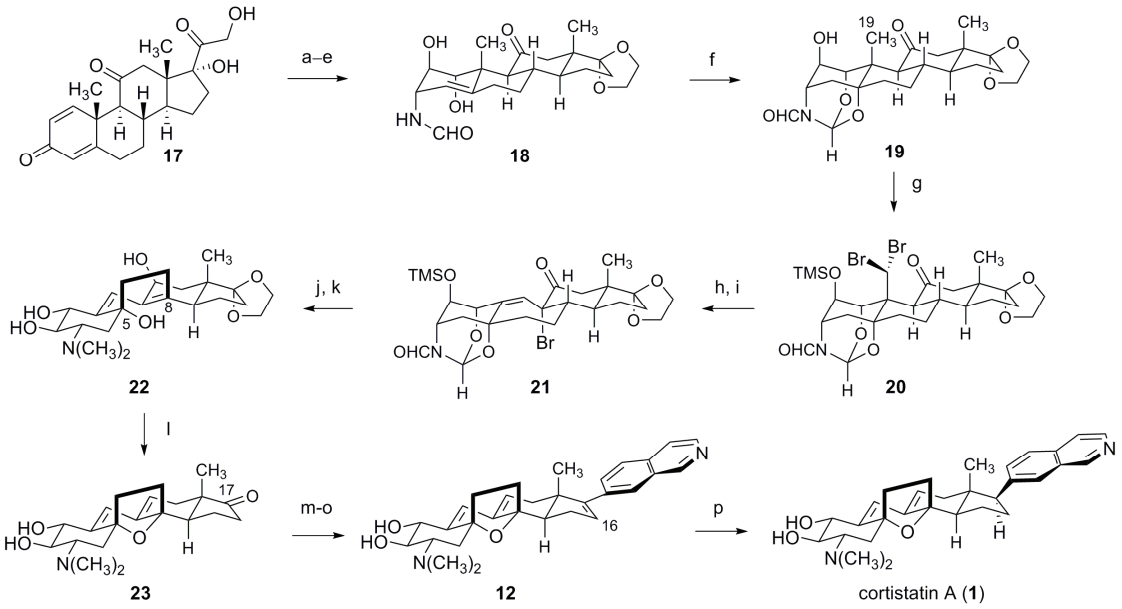
[30] Due to the limitation of this thesis, only several representative synthetic strategies towards cortistatins were selected and presented here, for additional references, see (a) Kurti, L.; Czako, B.; Corey, E. J. *Org. Lett.* **2008**, *10*, 5247–5250. (b) Kotoku, N.; Sumii, Y.; Hayashi, T.; Kobayashi, M. *Tetrahedron Lett.* **2008**, *49*, 7078–7081. (c) Sato, Y.; Kamiyama, H.; Usui, T.; Saito, T.; Osada, H.; Kuwahara, S.; Kiyota, H. *Biosci. Biotechnol. Biochem.* **2008**, *72*, 2992–2997. (d) Craft, D. T.; Gung, B. W. *Tetrahedron Lett.* **2008**, *49*, 5931–5934 (e) Dai, M. J.; Wang, Z.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, *49*, 6613–6616; (f) Dai, M. J.; Danishefsky, S. J. *Heterocycles* **2009**, *77*, 157–161. (g) Gung, B. W.; Craft, D. T. *Tetrahedron Lett.* **2009**, *50*, 2685–2687; see also reference 25, reference 27 and reference 28.

[31] Shenvi, R. A.; Guerrero, C. A.; Shi, J.; Li, C.-C.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7241–7243.

[32] For a later report in which the route was further optimized and scaled up, see: Shi, J.; Manolikakes, G.; Yeh, C.-H.; Guerrero, C. A.; Shenvi, R. A.; Shigehisa, H.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 8014–8027.

diazabicycloundec-7-ene (DBU) gave a cyclopropane intermediate, which was opened by exposure to samarium diiodide; the resulting samarium enolate intermediate was trapped with 2,4,4,6-tetrabromo-2,5-cyclohexadienone (TBCHD) to furnish bromide **21**. Allylic bromide elimination followed by alane reduction and then deprotection afforded intermediate **22**, setting the stage ready for the C5,C8 oxa-bridge closure. Bismuth(III) chloride was found to be an optimal Lewis acid which also effected deketalization after heating with water to afford cortistatinone **23**.[32] This ketone was converted to a vinyl iodide by Barton's method via a hydrazone and then cross-coupled with 7-

Scheme 1.1 Baran's Synthesis of Cortistatin A.



Reagents and conditions: (a) BH_3•THF; $NaIO_4$, acetone–H_2O, 0→23 °C; (b) ethylene glycol, *p*-TsOH•H_2O, $PhCH_3$, 110 °C, 92% (2 steps); (c) *t*-BuO_2H, DBU, THF, 23 °C, 72 h, 82%; (d) NH_4OAc, $Na(BH_3)CN$, CH_3OH, THF, 23 °C; then HCO_2Et, Et_3N, 54 °C, 73%; (e) TBAA, $Co(acac)_2$, PhH, 90 °C, 48%; (f) $Co(acac)_2$, $PhSiH_3$, O_2, THF, $HC(OCH_3)_3$, 23 °C; then TsOH•H_2O, 23 ºC; then K_2CO_3, CH_3OH, 65%; (g) $PhI(OAc)_2$, Br_2, CH_2Cl_2, –30 °C; then TMSCl, imidazole, 0 °C, 57%; (h) DBU, LiCl, THF, 23 °C, 85%; (i) SmI_2, DMPU–THF (1:9), 23 °C; then TBCHD, 23 °C; (j) LiBr, Li_2CO_3, DMF, 80 °C, 65% (2 steps); (k) AlH_3, THF, 23 °C; then K_2CO_3, CH_3OH, 23 °C, 85%; (l) $BiCl_3$, CH_3CN, 40°C; then water , 40°C, 73%; (m) N_2H_4, Et_3N, EtOH, 50 °C; (n) I_2, Et_3N, THF; (o) 7-(trimethylstannyl)isoquinoline, $Pd(PPh_3)_4$, CuCl, LiCl, DMSO, 23 °C, 53% (3 steps); (p) Raney Ni, *i*-PrOH, H_2O, 50 °C, 25% (50% brsm).

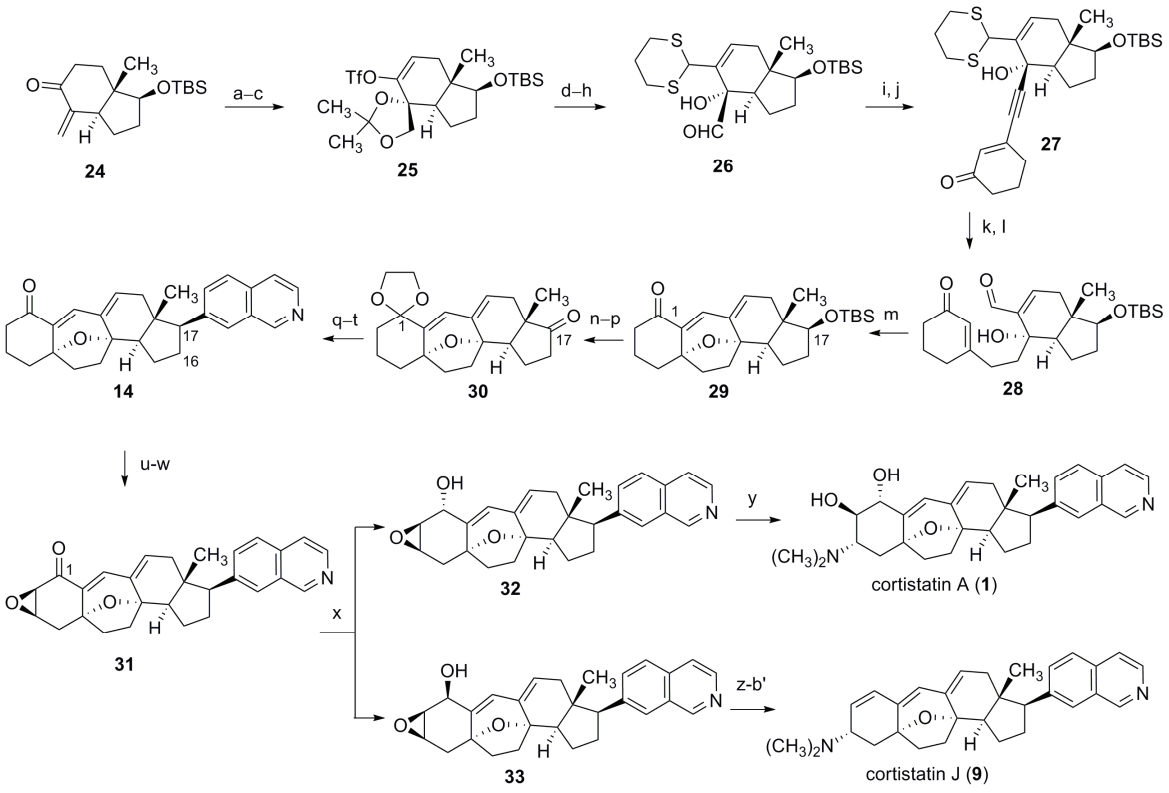
-(trimethylstannyl)isoquinoline. Finally, the trisubstituted olefin in Δ^{16}-cortistatin A (**12**) was reduced with Raney Nickel to complete the semi-synthesis of cortistatin A (**1**).

A couple months later, the Nicolaou–Chen group in Singapore completed the second synthesis of cortistatin A;[33] and in 2009, the same group reported the first synthesis of cortistatin J (Scheme 1.2).[26] Commencing from a known α-methylene ketone **24** prepared in five steps from Hajos-Parrish ketone, dihydroxylation, diol protection, and triflation gave intermediate **25**, which was elaborated to aldehyde **26** in another five steps. Subsequent acetylene formation and Sonogashira coupling provided alkyne **27**, the thioketal in which was cleaved and the triple bond hydrogenated, affording aldehyde **28**. An impressive oxa-Michael–Aldol–dehydration cascade reaction was subsequently accomplished by heating a solution of **28** with potassium carbonate in dioxane at 125°C to provide cortistatin core structure **29**. The C1 ketone was then temporally ketalized and the C17 *tert*-butyldimethylsilyl ether group was removed and oxidized to give ketone **30**. The isoquinoline substituent was incorporated at this stage by converting the C17 ketone to a vinyl triflate and Suzuki−Miyaura coupling with 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinoline. Selective hydrogenation of the C16,C17 tri-substituted olefin was achieved after deprotection of the C-1 ketal. The resulting ketone **14** underwent Saegusa desaturation and nucleophilic epoxidation to afford keto epoxide **31**, which was reduced under Luche conditions to give a 1:1 mixture of diastereomers **32** and **33**. **32** was treated with dimethylamine in the presence of titanium tetraisopropoxide to effect nucleophilic epoxide opening to afford cortistatin A (**1**); while **33** was converted to cortistatin J (**9**) in three steps: the epoxide was opened

[33] Nicolaou, K. C.; Sun, Y. P.; Peng, X. S.; Polet, D.; Chen, D. Y. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 7310–7313.

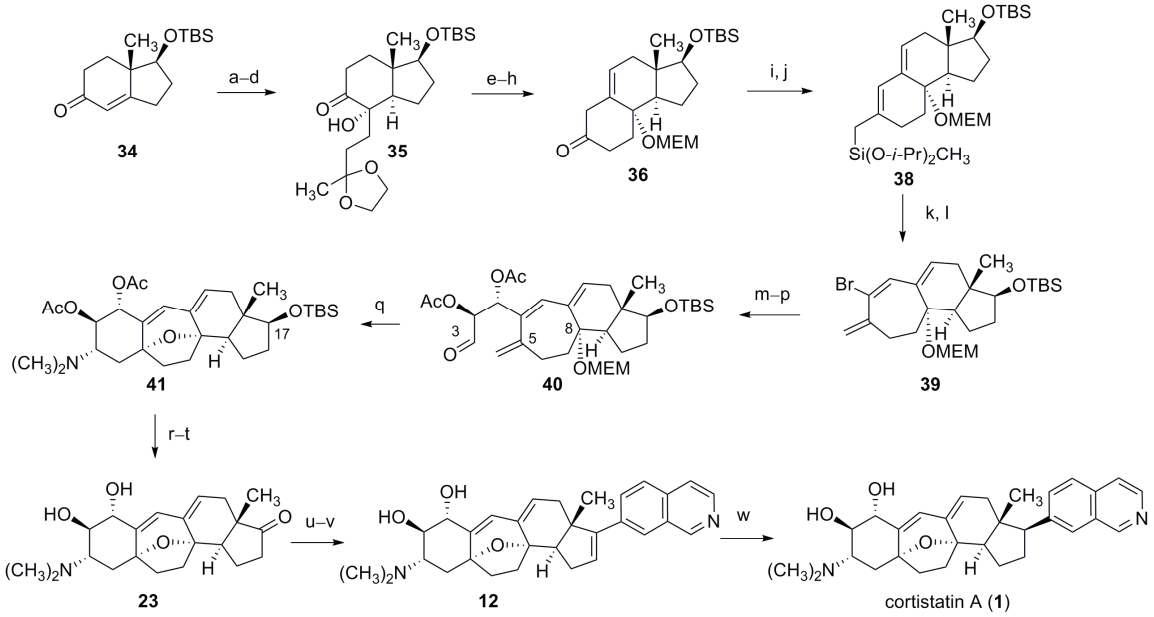
with dimethylamine in the presence of titanium tetraisopropoxide, the resulting *cis*-diol product was converted to a thiocarbonate and then eliminated with Corey−Winter's conditions.

Scheme 1.2 Nicolaou−Chen's Synthesis of Cortistatin A and Cortistatin J.



Reagents and conditions: (a) OsO_4, NMO, acetone–H_2O, 73%; (b) $(CH_3)_2C(OCH_3)_2$, *p*-TsOH, acetone, 87%; (c) NaHMDS, $PhNTf_2$, THF, 0 °C; (d) $Pd(PPh_3)_4$, Et_3N, CO, DMF–CH_3OH, 70 °C, 72% (2 steps); (e) DIBAL-H, $PhCH_3$, −78 °C, 79%; (f) DMP, $NaHCO_3$, CH_2Cl_2, 23 °C, 86%; (g) $HS(CH_2)_3SH$, BF_3•OEt_2, CH_2Cl_2, −78°C, 70%; (h) SO_3•Py, Et_3N, CH_2Cl_2–DMSO, 72%; (i) *p*-TsN_3, dimethyl-2-oxopropyl-phosphonate, K_2CO_3, CH_3CN, CH_3OH–THF–CH_3CN, 45% (2 cycles); (j) $Pd(PPh_3)_4$, CuI, Et_3N, 3-oxocyclohex-1-enyl trifluoromethanesulfonate, DMF, 85%; (k) IBX, DMSO, 0→23 °C, 81%; (l) Pd/$BaSO_4$, H_2, CH_3OH–THF (1:1), 64%; (m) K_2CO_3, dioxane, 125 °C, 52%; (n) $TMSO(CH_2)_2OTMS$, TMSOTf, CH_2Cl_2, −60→ −10 °C; (o) TBAF, THF, 56% (2 steps); (p) SO_3•Py, Et_3N, CH_2Cl_2–DMSO, 80%; (q) KHMDS, THF, −78 °C, then $PhNTf_2$; (r) 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinoline, $Pd(PPh_3)_4$, K_2CO_3, THF, 80 °C, 50% (2 steps); (s) *p*-TsOH, acetone–H_2O, 88%; t) Pd/C, H_2, CH_3OH, 23 °C, 50%; (u) TMSOTf , Et_3N, THF, −78→0 °C; (v) IBX•MPO, DMSO, 23 ºC, 6 h, 46% (2 steps); (w) *t*-BuO_2H, DBU, CH_2Cl_2, 0→23 °C, 70%; (x) $NaBH_4$, $CeCl_3$, CH_3OH, 0 °C, 80% (1:1 mixture of diastereomers **32** and **33**); (y) $(CH_3)_2NH$, Ti(O-*i*-Pr)$_4$, THF, 80 °C, 45%; (z) $(CH_3)_2NH$, Ti(O-*i*-Pr)$_4$, THF, 80 °C, 60%; (a') thiocarbonyl diimidazole, $PhCH_3$, 110 °C, 81%; (b') $P(OEt)_3$, 160 °C, 40%.

Scheme 1.3 Shair's Synthesis of Cortistatin A.



Reagents and conditions: (a) NaH, DMSO, 2-(2-bromoethyl)-2-methyl-1,3-dioxolane, 23 °C, 63%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (c) H_2, Pd/C, EtOAc, 23 °C; (d) *m*-CPBA, $NaHCO_3$, $PhCH_3$, −10 °C; then HF, THF–$PhCH_3$, 0 °C, 66% (4 steps); (e) MEMCl, *i*-$PrNEt_2$, 1,2-dichloroethane, 80 °C, 88%; (f) PPTS, acetone–water, 60 °C; (g) $NaOCH_3$, CH_3OH, 70 °C, 49% (2 steps); (h) $SOCl_2$, pyridine, CH_2Cl_2, −10 °C; (i) NaHMDS, −78 °C, $PhNTf_2$, 0 °C; (j) $CH_3(O\text{-}i\text{-}Pr)_2SiCH_2MgCl$ (**37**), $Pd(PPh_3)_4$, THF, 62% (3 steps); (k) $CHBr_3$, KO-*t*-Bu, hexane, 0 °C; (l) TASF, DMF, 80 °C, 66% (2 steps); (m) $TESOCH_2CH{=}CH\text{-}B(pin)$, $Pd(PPh_3)_4$, K_2CO_3, THF–H_2O, 80 °C, 84%; (n) $K_2OsO_4{\bullet}2H_2O$, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $CH_3SO_2NH_2$, *t*-BuOH–H_2O, 0 °C; (o) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 51% (2 steps); (p) HF•Py, THF; DMP, CH_2Cl_2; (q) $(CH_3)_2NH$, $ZnBr_2$, CH_3CN, 50 °C, 65% (3 steps); (r) TBAF, THF, 70 °C, 70%; (s) TPAP, NMO, CH_2Cl_2, 100%; (t) K_2CO_3, CH_3OH, 82%; (u) $N_2H_4{\bullet}H_2O$, Et_3N, EtOH, 80 °C; Et_3N, I_2, THF; (v) $Pd(PPh_3)_4$, 7-(trimethylstannyl)isoquinoline, LiCl, CuCl, DMSO, 60 °C, 61% (3 steps); (w) 2,4,6-triisopropylbenzenesulfonylhydrazide, Et_3N, THF, 60 °C, 20%.

In the fall of 2008, the Shair group at Harvard reported the third synthesis of cortistatin A (Scheme 1.3).[34] In the Shair synthesis, known enone **34** was alkylated with 2-(2-bromoethyl)-2-methyl-1,3-dioxolane and then converted to an extended silyl enol ether; subsequent hydrogenation and Rubottom oxidation afforded tertiary alcohol **35**. This alcohol was converted to ketone **36** in four steps (including methoxyethoxymethyl ether protection, deketalization, aldol reaction and dehydration), which was further transformed to an extended enol triflate and then cross-coupled with a Grignard reagent

[34] Lee, H. M.; Nieto-Oberhuber, C.; Shair, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 16864–16866.

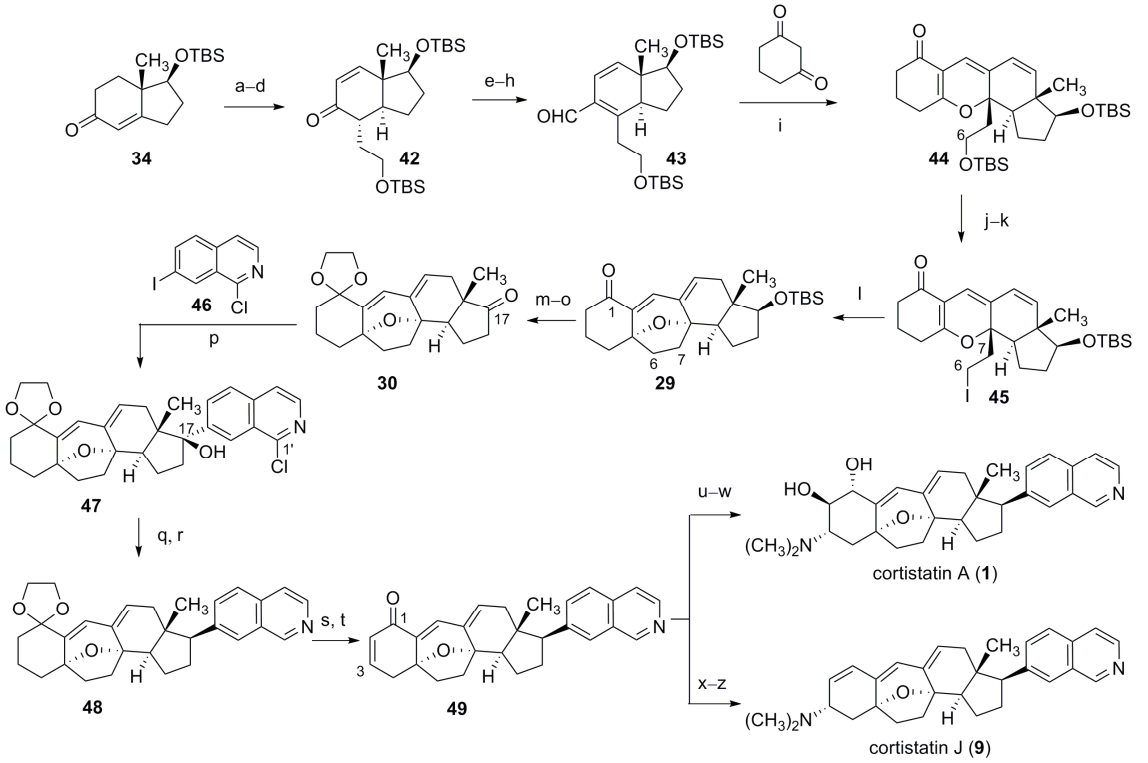
37 to give allylsilane **38**. Cyclopropane formation with dibromocarbene followed by its opening trigged by tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) furnished vinyl bromide **39**. Another palladium catalyzed cross-coupling, then selective Sharpless dihydroxylation and a couple functional group manipulations afforded aldehyde **40**. In the subsequent key step, a remarkable tandem aza-Prins-transannular etherification cascade was realized by heating aldehyde **40** with dimethylamine in the presence of zinc bromide, to provide compound **41** with a full cortistatin A ABC-ring skeleton. The C-17 *tert*-butyldimethylsilyl ether group was then cleaved and the secondary alcohol was oxidized; after deacetylation, the same cortistatinone **23** reported by the Baran group was obtained.[31] The isoquinoline appendage was then introduced by a similar Stille coupling between the **23**-derived vinyl iodide and 7-(trimethylstannyl)-isoquinoline to provide Δ^{16}-cortistatin A (**12**). Finally, diimide reduction of **12** afforded the natural product cortistatin A (**1**).

In 2011, the Hirama group from Tohoku University finished the total synthesis of cortistatin A and cortistatin J (Scheme 1.4).[35,36] Starting from enone **34**, alkylation, nickel boride reduction and Saegusa reaction provided intermediate **42**, which was converted to aldehyde **43** in four straightforward steps. In the subsequent key step, Knoevenagel condensation of **43** with cyclo-hexane-1,3-dione was followed by a tandem 6π-electrocyclization to afford intermediate **44**. C6 *tert*-butyldimethylsilyl ether was then selectively removed and the primary alcohol product was converted to iodide **45**. A radical cyclization initiated with triethylborane and oxygen closed the C6,C7 carbon

[35] Yamashita, S.; Iso, K.; Kitajima, K.; Himuro, M.; Hirama, M. *J. Org. Chem.* **2011**, *76*, 2408–2425.
[36] For two earlier synthetic studies reported by the Hirama group, see: (a) Yamashita, S.; Iso, K.; Hirama, M. *Org. Lett.* **2008**, *10*, 3413–3415; (b) Yamashita, S.; Kitajima, K.; Iso, K.; Hirama, M. *Tetrahedron Lett.* **2009**, *50*, 3277–3279.

bridge, affording the Nicolaou−Chen intermediate **29**.[33] **29** was then transformed to ketone **30**, and the isoquinoline ring was introduced to C17 ketone of **30** by the addition of an organocerium reagent derived from 1-chloro-7-iodoisoquinoline (**46**). The addition product **47** underwent radical deoxygenation via its 17-*O*-thiocarbamate to give intermediate **48** with C1'-chloride dehalogenated in the same operation. Deketalization

Scheme 1.4 Hirama's Synthesis of Cortistatin A and Cortistatin J.

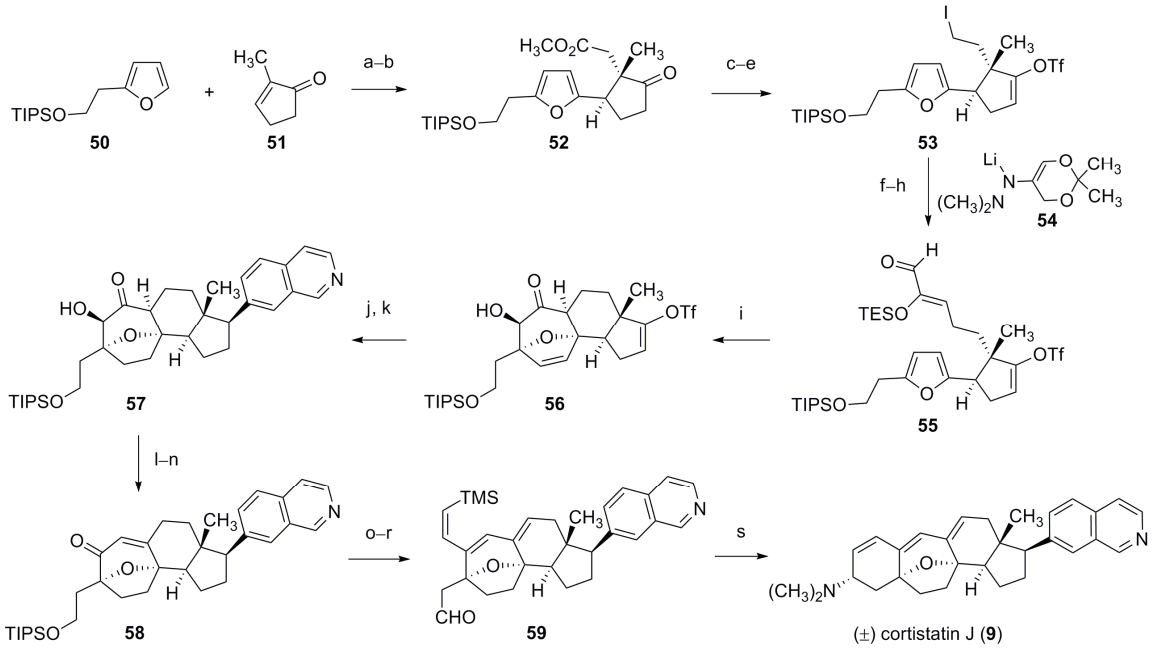


Reagents and conditions: (a) NaH, $TBSOCH_2CH_2I$, DMSO−THF, 23 °C, 53%; (b) $NiCl_2•6H_2O$, $NaBH_4$, CH_3OH, −70 °C, 60%; (c) TMSCl, $HN(TMS)_2$, NaI, CH_3CN, 23 °C; (d) $Pd(OAc)_2$, CH_3CN, 23 °C, 90% (2 steps); (e) Tf_2O, LDA, THF, −100→−90 °C, 95%; (f) $Pd(PPh_3)_4$, CO, Et_3N, CH_3OH–DMF, 55 °C, 90%; (g) DIBAL-H, $PhCH_3$, −78 °C; (h) DMP, $NaHCO_3$, CH_2Cl_2, 23 °C, 85% (2 steps); (i) cyclohexane-1,3-dione, piperdine, EtOAc, 23 °C, 87%, 5:1 dr; (j) HF•Py, THF, 23 °C; (k) I_2, PPh_3, imidazole, THF, 23 °C, 87% (2 steps); (l) Et_3B, $(TMS)_3SiH$, THF, −78 °C, 78%. (m) $TMSO(CH_2)_2OTMS$, TMSOTf, CH_2Cl_2, −60→ −20 °C; (n) TBAF, THF, 0 ºC; (o) DMP, $NaHCO_3$, CH_2Cl_2, 23 ºC, 73% (3 steps); (p) *n*-BuLi, $CeCl_3$, isoquinoline **46**, THF, −78 ºC, 99%; (q) KH, PhNCS, THF, 23 ºC; (r) AIBN, Bu_3SnH, $PhCH_3$, 90 ºC, 74% (2 steps); (s) $TsOH•H_2O$, acetone–H_2O, 71%. (t) LDA, Ph(Cl)S=N*t*-Bu, THF, −78 ºC, 80%; (u) *t*-BuO_2H, DBU, CH_2Cl_2, 0→23 °C, 75%; (v) $NaBH_4$, $CeCl_3$, CH_3OH, 0 °C, 51%; (w) $(CH_3)_2NH$, $Yb(OTf)_3$, THF, 80 °C, 48%; (x) $(CH_3)_2NH$, THF, 23 °C; (y) $LiAlH_4$, ether, 0 °C, 60% (two steps); (z) MsCl, Et_3N, THF, 0 °C; DBU, 23 °C, 42%.

and Mukaiyama unsaturation provided enone **49**, which was converted to cortistatin A (**1**) in three steps analog to the Nicolaou−Chen synthesis;[33] and converted to cortistatin J (**9**) also in three steps including dimethylamine conjugate addition, LAH reduction, and finally mesylation and elimination of the resulting C1 allylic alcohol.

In the summer of 2011, the Funk group from Pennsylvania State University reported a racemic synthesis of cortistatin J starting from furan **50** (Scheme 1.5).[37] This furan was first metallated and added conjugatively to enone **51**; the resulting enolate intermediate was trapped with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and

Scheme 1.5 Funk's Synthesis of (±)-Cortistatin J.



Reagents and conditions: (a) *n*-BuLi; $AlMe_3$; TMSOTf, **51**; (b) CH_3Li; $ICH_2CO_2CH_3$, 75% (two steps); (c) NaHMDS, $PhNTf_2$; (d) DIBAL-H, 82% (two steps); (e) PPh_3, I_2; (f) **54**+**55**; AcOH, H_2O, 75%; (g) NaHMDS, TESCl, 94%; (h) $PhCH_3$, 100 °C, quant.; (i) 50 mol% TfOH, CH_2Cl_2, −78 °C; pyridine, CH3OH, 79%; (j) $Pd(PPh_3)_4$, 7-(trimethylstannyl)isoquinoline, LiCl, CuCl, 70%; (k) $KO_2N{=}NCO_2K$, AcOH, 97%; (l) DMSO, $(COCl)_2$, Et_3N, 81%; (m) NaH; $PhNTf_2$, 83%; (n) Bu_3SnH, $Pd(PPh_3)_4$, 70% (o) LiHMDS, HMPA, $PhNTf_2$, 81%; (p) 6N HCl, 81%; (q) (Z)-TMS-CH=CH-BF_3K, Cs_2CO_3, $Pd(PPh_3)_4$, 84%; (r) Py·SO_3, DMSO, Et_3N, 75%; (s) $(CH_3)_2NH{\cdot}HCl$, CH_3CN, 60 °C, 90%.

[37] Nilson, M. G.; Funk, R. L. *J. Am. Chem. Soc.* **2011**, *133*, 12451−12453.

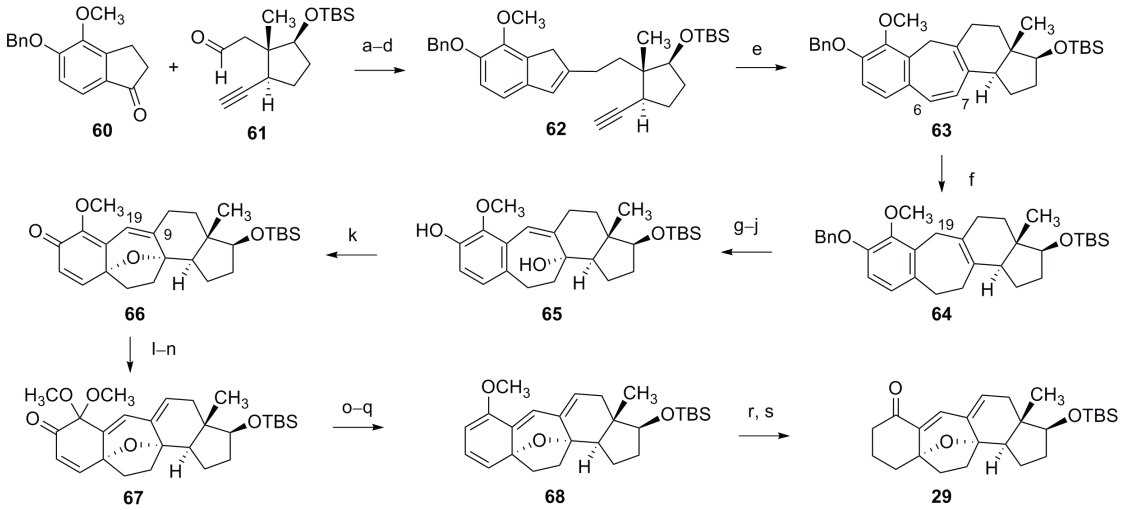
the silyl enol ether product was subsequently converted to primary iodide **53** in a four-step sequence (including alkylation, triflation, DIBAL-H reduction, and iodination). An azaenolate **54** was then alkylated with this iodide, and the resulting alkylation product underwent triethylsilyation formation and thermal retro-cycloadditon to afford intermediate **55**. A key [4+3] cycloaddition to construct the cortistatin core oxabicyclo[3.2.1]octene structure was triggered by treating a solution of **55** in dichloromethane with trflic acid (0.5 equiv) at −78°C, affording intermediate **56** in good yield. The isoquinoline moiety was then introduced by Stille cross-coupling with 7-(trimethylstannyl)isoquinoline, and a global diimide reduction afforded tetrahydrofuran **57**. Swern oxidation, triflation, and palladium catalyzed triflate reduction with ammonium formate provided enone **58**. This enone underwent another triflation, then Suzuki−Miyaura coupling, and a couple functional group manipulations to provide aldehyde **59** with a (*Z*)-vinyl silane installed. Finally, a solution of aldehyde **59** in acetonitrile was treated with excess dimethylamine hydrochloride at 60°C to effect a stereoselective A-ring closure, affording (±)-cortistatin J (**9**) as a single diastereomer.

The Sarpong group at Berkeley completed a formal synthesis of racemic cortistatins in 2010 (Scheme 1.6).[38] Starting from aldol condensation between indanone **60** and aldehyde **61**, reduction and subsequent elimination afforded indene **62**. This indene underwent a platinum dichloride catalyzed enyne cycloisomerization, a methodology previously developed in the Sarpong group, affording diene **63**. The C6,C7 disubstituted double bond in **63** was then selectively reduced under diimide reduction conditions to give **64**; the remaining tetra-substituted olefin was epoxidized with sodium

[38] (a) Simmons, E. M.; Hardin-Narayan, A. R.; Guo, X.; Sarpong, R. *Tetrahedron*, **2010**, 66, 4696–4700 (b)Simmons, E. M.; Hardin, A. R.; Guo, X.; Sarpong, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6650–6653.

bicarbonate neutralized 3-chloroperoxybenzoic acid (*m*CPBA), and the epoxide product was eliminatively opened with *n*-butyllithium at the benzylic position to afford allylic alcohol **65** (obtained after a couple protection group manipulations). This phenol **65** was subsequently oxidatively cyclized by exposure to bisacetoxyiodobenzene, a hypervalent iodine reagent, to provide cortistatin core structure **66**. Selective epoxidation of C9,C19 trisubstituted olefin was followed by acidic opening of the epoxide product and then elimination of the resulting C9 allylic alcohol, affording diene **67**. The C2 enone was then reduced under Luche conditions and temporarily protected; a palladium catalyzed, ammonium formate promoted reduction and rearrangement provided intermediate **68**. Finally, hydrogenation and isomerization afforded Nicolaou−Chen's intermediate **29**.[33]

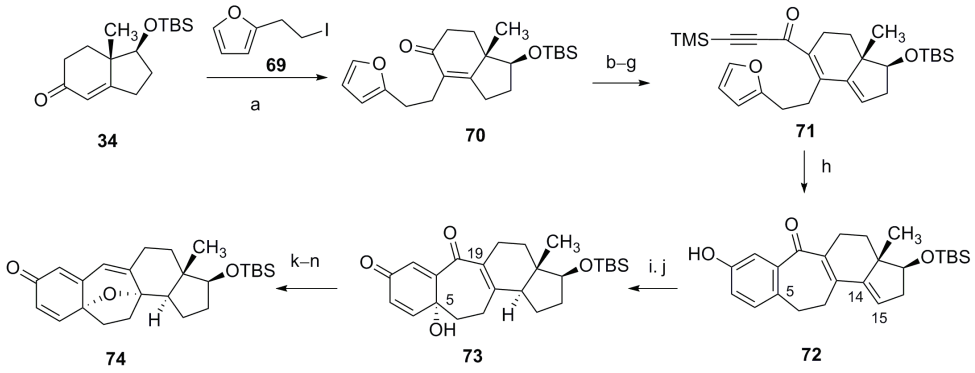
Scheme 1.6 Sarpong's Formal Synthesis of (±)-Cortistatins.



Reagents and conditions: (a) KOH, EtOH–CH_2Cl_2, 76%; (b) K-Selectride, THF, –78→23 °C; (c) $NaBH_4$, CH_3OH–CH_2Cl_2, 0 °C; (d) $KHSO_4$, $PhCH_3$, 50 °C, 67% (3 steps); (e) $PtCl_2$, PhH, 50 °C, 82%; (f) $TsNHNH_2$, Et_3N, 1,2-DCE, 65 °C, (2 cycles); (g) Na/naphthalene, DME, 23 °C, 77% (2 steps); (h) TESCl, imidazole, DMF, 23 °C; (i) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 53% (2 steps); (j) *n*-BuLi, THF, 0 °C; (k) $PhI(OAc)_2$, CH_2Cl_2–*i*-PrOH–TFE, −78 °C, 57% (2 steps). (l) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0°C; (m) CSA, CH_2Cl_2-CH_3OH, 0 °C; (n) TFAA, DMAP, DCE-Et_3N, 23→60°C , 58% (three steps); (o) $NaBH_4$, $CeCl_3$, CH_3OH, 0 °C ; (p) $(BocO)_2O$, DMAP, DCE, 40 °C, 69% (two steps); (q) $Pd(dppf)Cl_2$, NH_4CO_2H, 23→60°C;(r) H_2 (100 psi), $Rh(PPh_3)_3Cl$, PhH; (s) 1% aq HCl, THF, 0→23°C, 77% (three steps).

The Yang-Li group from Peking University also reported a formal synthesis of cortistatins in early 2011 (Scheme 1.7).[39] Enone **34** was first alkylated with iodide **69** to provide intermediate **70**, which was subsequently transformed to alkyne **71** in five steps. An intramolecular furan Diels−Alder reaction was catalyzed by ethylaluminium dichloride to forge the 7-membered B ring, providing phenol product **72**. The C14,C15 double bond was then selectively hydrogenated, and a tertiary hydroxyl group was introduced at C5 with modest diastereoselectivity by bisacetoxyiodobenzene promoted oxidative dearomatization of A-ring phenol in the presence of water, affording dienone intermediate **73**. Finally, sodium acetate triggered oxa-Michael addition, selective reduction of C19 ketone, and subsequent mesylation and elimination of the C19 allylic alcohol product furnished Myers' intermediate **74**.[40]

Scheme 1.7 Yang-Li's Formal Synthesis of Cortistatins.

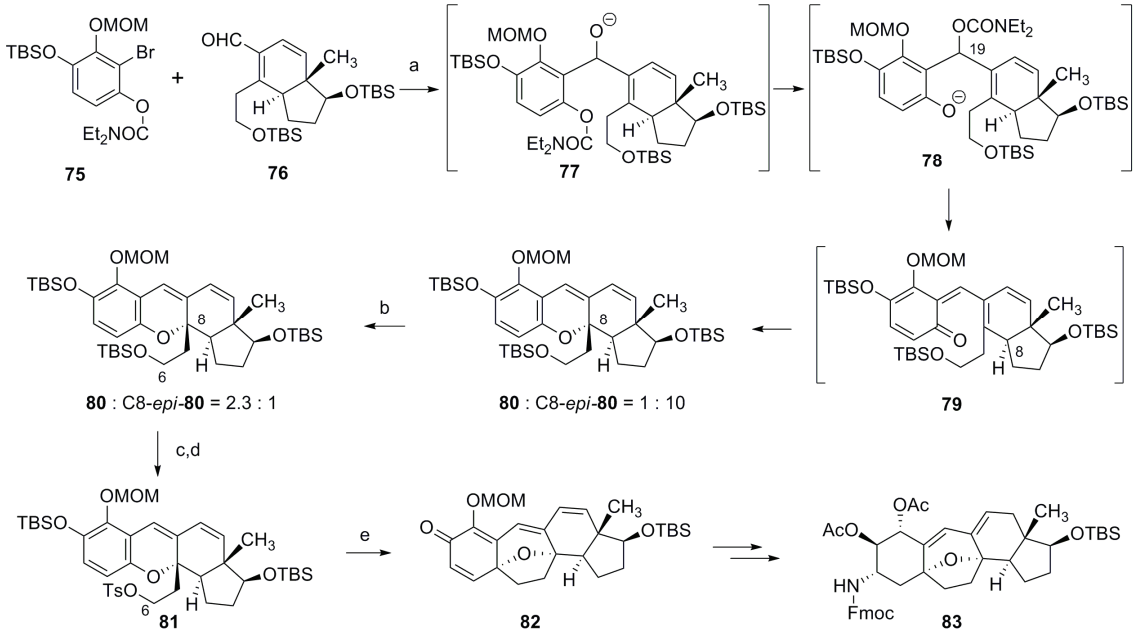


Reagents and conditions: (a) NaH, **69**, DMSO, 46%; (b) collidine, Tf_2O; (c) $Pd(OAc)_2$, PPh_3, CO, CH_3OH, 76% (two steps); (d) DIBAL-H, −78 °C, 90%; (e) MnO_2, CH_2Cl_2, 94%; (f) TMSC≡CH, *n*-BuLi, THF, −78°C, 95%; (g) MnO_2, CH_2Cl_2, 91%; (h) $EtAlCl_2$, CH_2Cl_2, −78→0 °C, 51%; (i) $Pd/BaSO_4$, H_2 (1 atm), 60%; (j) BAIB, CH_3CN-H_2O, 60%, **73**:5-*epi*-**73** = 1:1.5; (k) $NaOAc{\cdot}3H_2O$, EtOH, 50°C, 70%; (l) $LiBHEt_3$, THF, −78 °C; (m) MsCl, Et_3N, DMAP, CH_2Cl_2; (n) LiBr, Li_2CO_3, DMF, 100°C, 28% (three steps).

[39] (a) Fang, L.; Chen, Y.; Huang, J.; Liu, L.; Quan, J.; Li, C.-C.; Yang, Z. *J. Org. Chem.* **2011**, *76*, 2479–2487; (b) Liu, L. Z.; Gao, Y. X.; Che, C.; Wu, N.; Wang, D. Z.; Li, C. C.; Yang, Z. *Chem. Commun.* **2009**, 662–664.

[40] Flyer, A. N.; Si, C.; Myers, A. G. *Nature Chemistry* **2010**, *2*, 886–892.

Scheme 1.8 Danishefsky's Approach to Cortistatins *via* a Sniekus Reaction Cascade.



Reagents and conditions: (a) *t*-BuLi, **76**, Et_2O, −78 °C, then 130 °C, 50%, **80** : C8-epi-**80** = 1 : 10; (b) 192→198 °C, **80** : C8-epi-**80** = 2.3 : 1; (c) I_2, CH_3OH, 54%; (d) TsCl, Py, DMAP, CH_2Cl_2, 0→23 °C, 95%; (e) TBAF, THF, 70 °C, 94%.

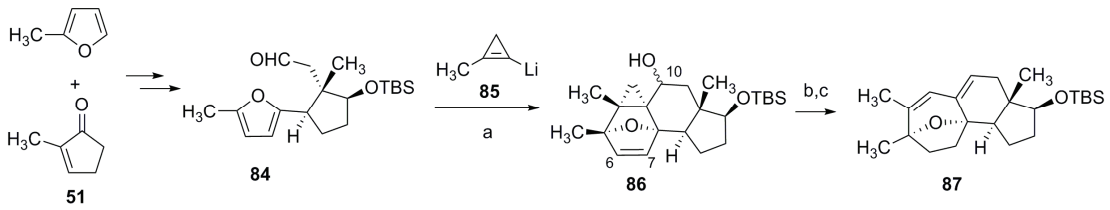
The Danishefsky group developed two different strategies to construct the cortistatin core structure[30e,f] and the approach via a Sniekus reaction initiated cascade is presented here (Scheme 1.8).[41] Lithiated aryl bromide **75** added to aldehyde **76** at −78 °C to form intermediate **77**; the crude reaction mixture was then heated to 130 °C to trigger a Sniekus rearrangement; the C19 carbamate of the resulting intermediate **78** was believed to eliminate at this temperature and the resulting *o*-quinonemethide **79** underwent a tandem 6π-electrocyclization to afford *2H*-pyran **80**. The C8-*epi* isomer which dominated in the product mixture, was mostly epimerized to the desired isomer by heating at 192−198 °C. Selective desilyation and tosylation at C6 provided compound **81**, which was alkylatively dearomatized by the treatment with tetra-*n*-butylammonium fluoride in

[41] (a) Wang, Z.; Dai, M. J.; Park, P. K.; Danishefsky, S. J. *Tetrahedron* **2011**, *67*, 10249−10260; (b) Dai, M. J.; Danishefsky, S. J. *Tetrahedron Lett.* **2008**, *49*, 6610–6612.

refluxing tetrahydrofuran, affording cortistatin core structure **82**. This enone was then elaborated to **83** in a couple of steps, which possessed a fully functionalized cortistatin A ABC-ring system.

The Magnus group developed an efficient approach to (±)-cortistatin BCD rings commencing from Lewis acid promoted addition of 2-methylfuran to enone **51** (Scheme 1.9).[42] The addition product was then converted to aldehyde **84** in a couple of steps. Cyclopropenyllithium **85** added to this aldehyde at −50 °C; upon warming the reaction mixture to 23 °C, a cyclopropene-furan [2+4] cycloaddition proceeded to afford compound **86** as a 1:1 mixture of diastereomers at C10. Hydrogenation of C6,C7 olefin with Adam's catalyst followed by cyclopropylcarbinyl rearrangement triggered by triflation of the C10 hydroxyl group provided compound **87** in good yield with a cortistatin BCD-ring skeleton.

Scheme 1.9 Magnus's Approach to (±)-Cortistatin BCD Rings *via* Cyclopropene-Furan [2+4] Cycloaddition followed by Cyclopropylcarbinyl Rearrangement.



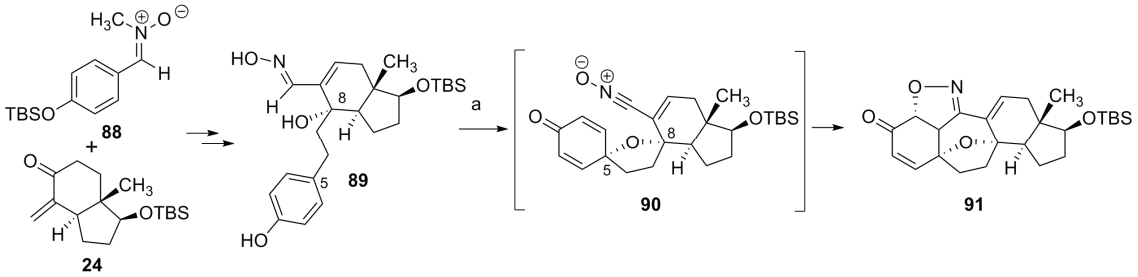
Reagents and conditions: (a) **85**, −50→23 °C, 85%, 1:1 dr at C-10; (b) H_2, $PtO_2.H_2O$, THF-EtOH, AcOH (cat.), 98%; (c) Tf_2O, DTBMP, CH_2Cl_2, 0→23 °C, 70%.

The Sorensen synthesis started from a [3+2] dipolar cycloaddition of nitrone **88** and α-methylene ketone **24**, and the addition product was transformed to oxime **89** in a

[42] Magnus, P.; Littich, R. *Org. Lett.* **2009**, *11*, 3938–3941.

couple of steps (Scheme 1.10).[43] Upon treatment of a solution **89** in trifluoroethanol with bisacetoxyiodobenzene at 23 °C, the phenol underwent oxidative dearomatization to form the C5,C8 oxa-bridge and the oxime was also oxidized to give nitrile oxide **90**; when this crude reaction mixture was further heated to 50 °C, an intramolecular [3+2] dipolar cycloaddition proceeded, yielding compound **91** with the cortistatin pentacyclic core structure.

Scheme 1.10 Sorensen's Approach to Cortistatin Core Structure *via* Hypervalent Iodine-Induced Double Annulation.

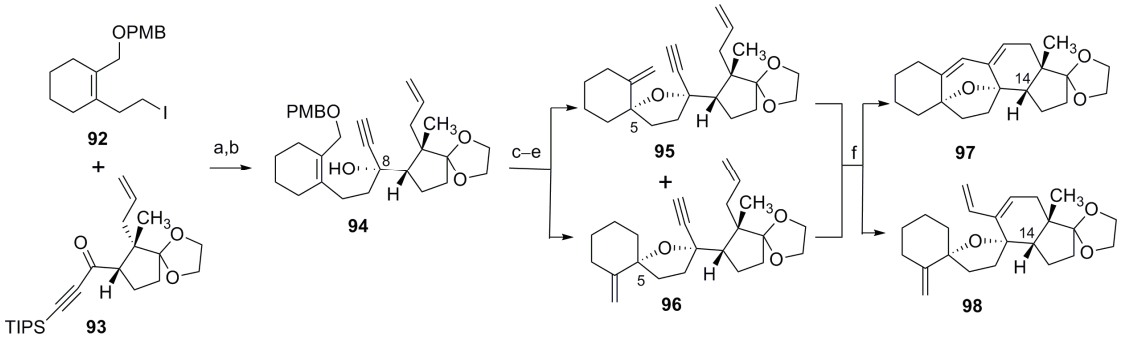


Reagents and conditions: (a) $PhI(OAc)_2$, CF_3CH_2OH, 23 °C; then 50 °C, 80%.

The Stoltz group approached the pentacyclic cortistatin core structure using a cascade enyne-ene metathesis strategy (Scheme 1.11).[44] Lithiated iodide **92** was added to ketone **93**, affording a tertiary alcohol **94** after desilyation. The C5,C8 oxa-bridge was constructed by a magnesium bromide catalyzed S_N2' reaction, providing tetrahydrofuran **95** and **96** as a 1:1 mixture of diastereomers at the C5 position. When this mixture was subjected to Grubbs second-generation catalyst, the desired diastereomer **95** underwent the expected enyne-ene metathesis to yield the 14-*epi*-cortistatin core structure **97**, while the undesired diastereomer **96** stopped at the diene stage to afford compound **98**.

[43] Frie, J. L.; Jeffrey, C. S.; Sorensen, E. J. *Org. Lett.* **2009**, *11*, 5394–5397.
[44] Baumgartner, C.; Ma, S.; Liu, Q.; Stoltz, B. *Org. Biomol. Chem.* **2010**, *8*, 2915–2917.

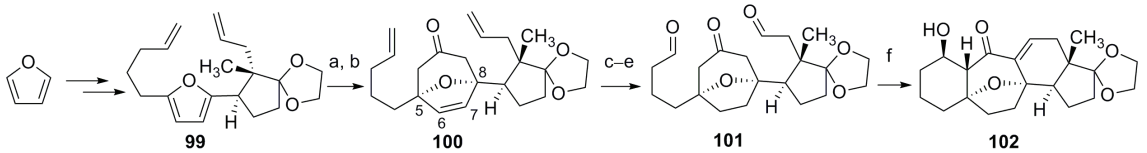
Scheme 1.11 Stoltz's Approach to 14-*epi*-Cortistatin Core *via* Enyne-ene Metathesis.



Reagents and conditions: (a) *t*-BuLi, **93**, Et_2O-THF, –78 °C; (b) TBAF, THF, 25 °C, 77% (two steps), **94**: 8-*epi*-**94** = 2.2 : 1; (c) DDQ, CH_2Cl_2-H_2O, 25 °C, 75%; (d) Ac_2O, pyridine, CH_2Cl_2, 25 °C, 94%; (e) $MgBr_2 \cdot Et_2O$, 2,6-DTBP, PhH-CH_3CN, 80°C, 79%, **95** : **96** = 1 : 1; (f) Grubbs-II, CH_2Cl_2, 25 °C, 37% of **97** and 44% of **98**.

The Zhai group constructed a racemic cortistatin core structure also starting from furan (Scheme 1.12).[45] The core oxabicyclo[3.2.1]octene structure was constructed by an intermolecular [4+3] cycloaddition of 2,5-disubstituted furan **99** with 1,1,3-trichloroacetone and then zinc-copper mediated dehalogenation to give ketone **100**. Following bis-dihydroxylation of the two terminal olefins, hydrogenation of the remaining C6,C7 double bond, and bis-vicinal diol cleavages afforded ketodialdehyde **101**. This aldehyde then underwent a double, intramolecular aldol reaction upon treating with potassium carbonate to furnish the cortistatin core structure **102**.

Scheme 1.12 Zhai's Approach to (±)-Cortistatin Core *via* Double Aldol Reaction.

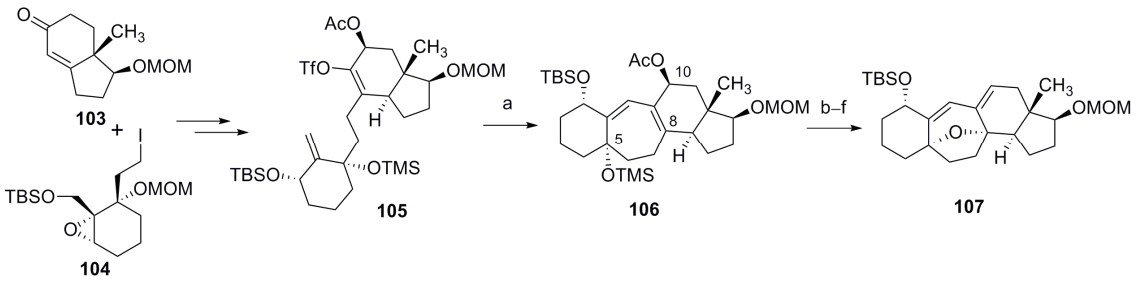


Reagents and conditions: (a) $Cl_2CHCOCH_2Cl$, Et_3N, $(CF_3)_2CHOH$; (b) Zn-Cu, NH_4Cl, CH_3OH, 46%; (c) OsO_4, NMO, acetone, H_2O; (d) H_2, Pd/C, EtOH; (e) $NaIO_4$, acetone, H_2O, 68% (three steps); (f) K_2CO_3, CH_3OH, 23 °C, 82%.

[45] Yu, F.; Li, G.; Gao, P.; Gong, H.; Liu, Y.; Wu, Y.; Cheng. B.; Zhai, H. *Org. Lett.* **2010**, *12*, 5135–5137.

The Kobayashi group (the isolation chemists) also developed several different strategies to construct the cortistatin core structure[28,30b] and their intramolecular Heck approach is described here (Scheme 1.13).[46] In this approach, the Hajos−Parrish ketone derived enone **103** was alkylated with primary iodide **104**, and in a couple steps transformed to triflate **105**. Intramolecular 7-endo Heck reaction was catalyzed by tris(dibenzylidene-acetone)dipalladium(0) and the ligand 1,3-bis(diphenylphosphino)-propane (dppp) in the presence of cesium acetate and tetra-*n*-butylammoniumacetate to afford intermediate **106**. After C5 desilyation, C10 deacetylation and oxidation, the oxa-bridge was then constructed by acid catalyzed, intramolecular oxa-Michael addition of the C5 tertiary alcohol to enone at C8 position. Finally, diene **107** was obtained after sodium borohydride reduction of C10 ketone and then Burgess elimination of the resulting secondary alcohol.

Scheme 1.13 Kobayashi's Approach to Cortistatin Core *via* Intramolecular Heck Reaction.



Reagents and conditions: (a) $Pd_2(dba)_3$, dppp, CsOAc, *n*-Bu_4NOAc, DMF, 70 °C, 56%; (b) TBAF, THF, 0 °C, 88%; (c) DIBAL, CH_2Cl_2, −78 °C, 94%; (c) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C, 81%; (e) CSA, THF, 0 °C, 60%; (f) $NaBH_4$, CH_3OH, 0 °C, 83%; (g) Burgess' reagent, toluene, 85 °C, 62%.

[46] Kotoku, N.; Sumii, Y.; Kobayashi, M. *Org. Lett.* **2011**, *13*, 3514–3517.

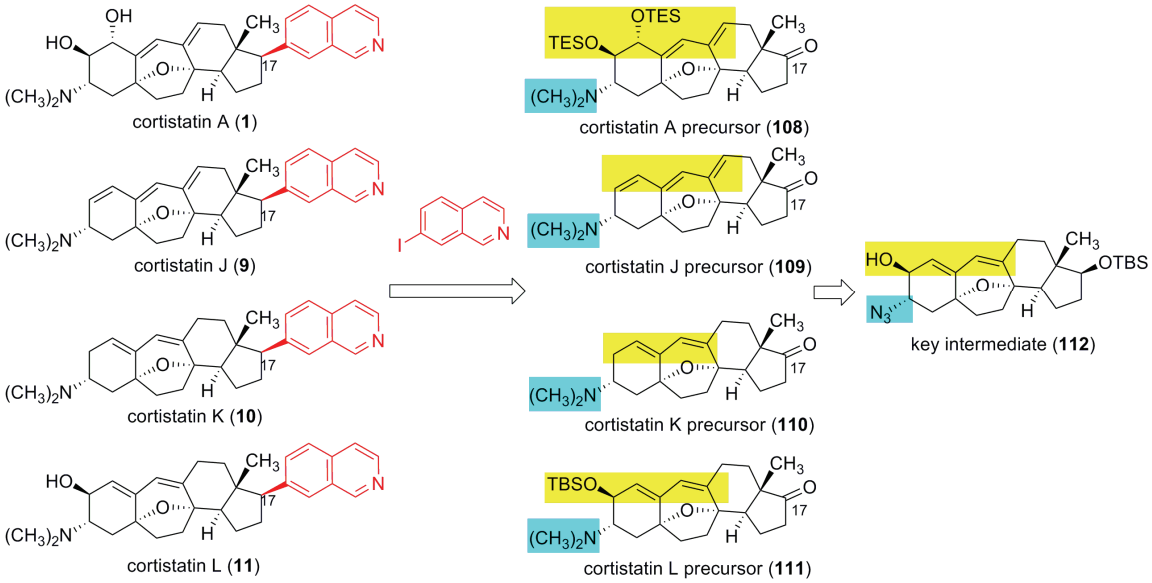
A Divergent Synthetic Strategy towards the Cortistatins

In our synthetic planning, we wished to develop a general approach that would allow us to access not only different members of cortistatin natural products, but also a diverse array of cortistatin analogs and biological probes. We envisioned that this goal could be achieved by efficient preparation of a suitable key intermediate which could be easily diversified to different cortistatin precursors,[47] and then installing the isoquinoline moiety at the final stage in order to maximize the possibility of diversification on this important ring substituent (see SAR data for details).

With these principles in mind, we believed that the isoquinoline substituent could be introduced to different C17-keto cortistatin precursors **108**, **109**, **110**, and **111** under suitable conditions to afford the final products (Figure 1.4). In order to access these different cortistatin precursors, we identified azido alcohol **112** as an appropriate candidate for the key intermediate: it possesses the pentacyclic core structure of cortistatins; the azido group at C3 provides a versatile handle for the introduction of the dimethylamino group in the natural cortistatins, as well as other nitrogen-containing functional groups in analog preparation; in addition, the C2 allylic alcohol and northern diene moiety should be readily transformed to obtain diverse cortistatin ABC-ring substitution patterns; to meet the requirements as a key intermediate, what we need would be to develop a robust and scalable route to prepare this azido alcohol.

[47]The Myers group has used similar principles in the preparation of a number of natural products and their analogs, including tetracycline,[a,b,c] avrainvillamide,[d,e] and trioxacarcins,[f] see: (a) Charest, M.; Lerner, C. D.; Brubaker, J. D.; Siegel, D. R.; Myers, A. G. *Science*, **2005**, *308*, 395–398. (b) Sun, C.; Wang, Q.; Brubaker, J. D.; Wright, P. M.; Lerner, C. D.; Noson, K.; Charest, M.; Siegel, D. R.; Wang, Y. M.; Myers, A. G. *J. Am. Chem. Soc*. **2008**, *130*, 17913–17927;(c) Wright, P. M.; Myers, A. G. *Tetrahedron* **2011**, *67*, 9853–9869; (d) Herzon, S. B.; Myers, A. G. *J. Am. Chem. Soc*. **2005**, *127*, 5342–5344. (e) Wulff, J. E.; Siegrist, R.; Myers, A. G. *J. Am. Chem. Soc*. **2007**, *129*, 14444–14451; (f) Svenda, J.; Hill, N.; Myers, A. G. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 6709–6714.

Figure 1.4 Syntheses of Cortistatins by Late Stage Introduction of Isoquinoline Moiety to 17-Keto Cortistatin Precursors Derived from a Common Key Intermediate **112**.

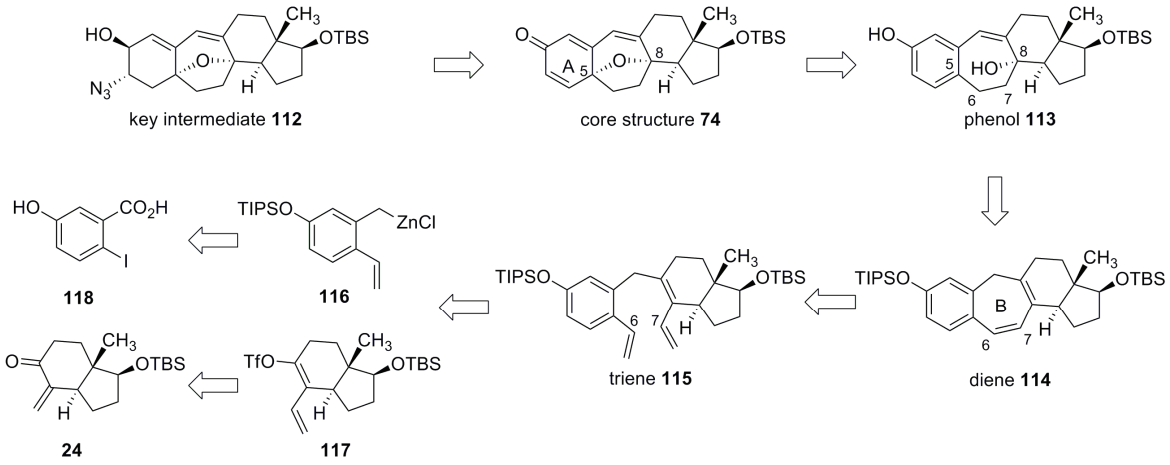


Retrosynthetically, this azido alcohol **112** could be derived from a cyclohexadienone **74** by selectively functionalizing the A-ring enone moiety (Figure 1.5). This cortistatin core structure **74** could be further simplified to phenol **113** by installing the C5,C8 oxa-bridge via oxidative dearomatization, a strategy independently conceived and previously demonstrated by Sarpong and coworkers, as well as others.[30f,38,42] Phenol **113** could be prepared from diene **114**, and the seven-membered B-ring in **114** could be constructed from triene **115** by ring-closing metathesis. Triene **115** could be in turn assembled from a benzylzinc reagent **116** and an enol triflate **117** via Negishi cross-coupling. Benzylzinc reagent **116** could be obtained from a known phenyl iodide **118**,[48]

[48] Moss, R. A.; Alwis, K. W.; Shin, J. S. *J. Am. Chem. Soc.* **1984**, *106*, 2651–2655.

while the enol triflate **117** could be synthesized from a known α-methylene ketone **24** derived from Hajos-Parrish ketone.[49,50]

Figure 1.5 Retrosynthetic Analysis of Key Intermediate **112**.



In this thesis, Chapter 2 presents an efficient synthesis of key intermediate **112** and diversification of this azido alcohol to different cortistatin precursors **108**, **109**, **110**, and **111**, representing each of the four ABC-ring substitution patterns in natural cortistatins; Chapter 3 details the conversion of these cortistatin 17-keto precursors to different cortistatin natural products as well as unnatural cortistatin analogs using a generally applicable isoquinoline-addition-radical-deoxygenation sequence; and Chapter 4 describes a versatile methodology to synthesize a diverse array of substituted isoquinolines, allowing the preparation of cortistatin analogs with isoquinoline modifications.

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[49] (a) Isaacs, R. C. A.; Digrandi, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 3938–3941; (b) Micheli, R. A.; Hojos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Sciamanna, W.; Scott, M. A.; Wehrli, P. A. *J. Org. Chem.* **1975**, *40*, 675–681.

[50] This α-methylene ketone **24** was also used by the Nicolaou group and the Sorensen group independently in the synthesis of cortistatins: see: Ref 33 and Ref 43.

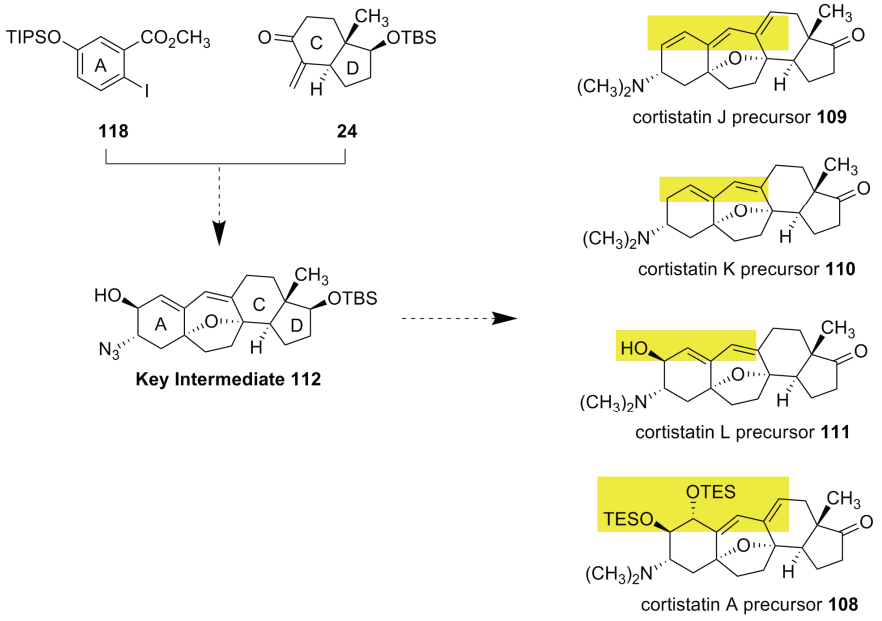
Chapter 2

Synthesis of Cortistatin Precursors from a Common Key Intermediate

Introduction

As outlined in Chapter 1, this chapter presents an efficient synthesis of the azido alcohol **112** as the key intermediate on gram quantities starting from A-ring precursor **118** and CD-ring precursor **24** (Figure 2.1). This key intermediate was subsequently converted to different cortistatin 17-keto precursors **108**, **109**, **110**, and **111**, representing all four natural cortistatin ABC-ring substitution patterns.

Figure 2.1 Converting Key Intermediate **112** to Different Cortistatin Precursors.



Synthesis of the Key Intermediate Azido Alcohol

Graduate student Dr. Alec Flyer developed an efficient synthesis of the cortistatin core structure **74** (Scheme 2.1).[1] I was able to further optimize and scale up this route to produce this cyclohexadienone on gram quantities. Benzyl bromide **119** was prepared in amounts up to 47 g by a straightforward five-step sequence [including methylation, phenol protection, Negishi cross-coupling, diisobutylaluminium hydride (DIBAL-H) reduction, and bromination] from a known phenyl iodide **118**,[2] and then transformed to the *o*-vinyl benzylzinc reagent **116** by magnesium insertion and transmetallation with zinc chloride. Meanwhile, a known α-methylene ketone **24**[3,4] was subjected to a phosphorniosilylation-Wittig reaction sequence to afford the α-vinyl triethylsilyl enol ether **120**,[5] which was then converted to enol triflate coupling partner **117** on a 15-g scale by using Corey's triflation conditions.[6]

Coupling of the enol triflate **117** with the benzylzinc reagent **116** was achieved in the presence of tris(dibenzylideneacetone)dipalladium (0.045 equiv) and the ligand 2-dicyclohexylphosphino-2′,6′-dimethoxy-biphenyl (S-Phos, 0.18 equiv) in a mixture of *N*-methylpyrrolidone, tetrahydrofuran, and ether (the latter two from the preparation of the

[1] For another approach to the same cyclohexadienone structure, see: Flyer, A. N. (2010) *A Synthetic Route to Cortistatin A and L.* Ph.D. thesis, Harvard University.

[2] Iodide **118** was prepared in one step from commercial available 2-amino-5-hydroxylbenzoic acid as reported: Moss, R. A.; Alwis, K. W.; Shin, J. S. *J. Am. Chem. Soc.* **1984**, *106*, 2651–2655.

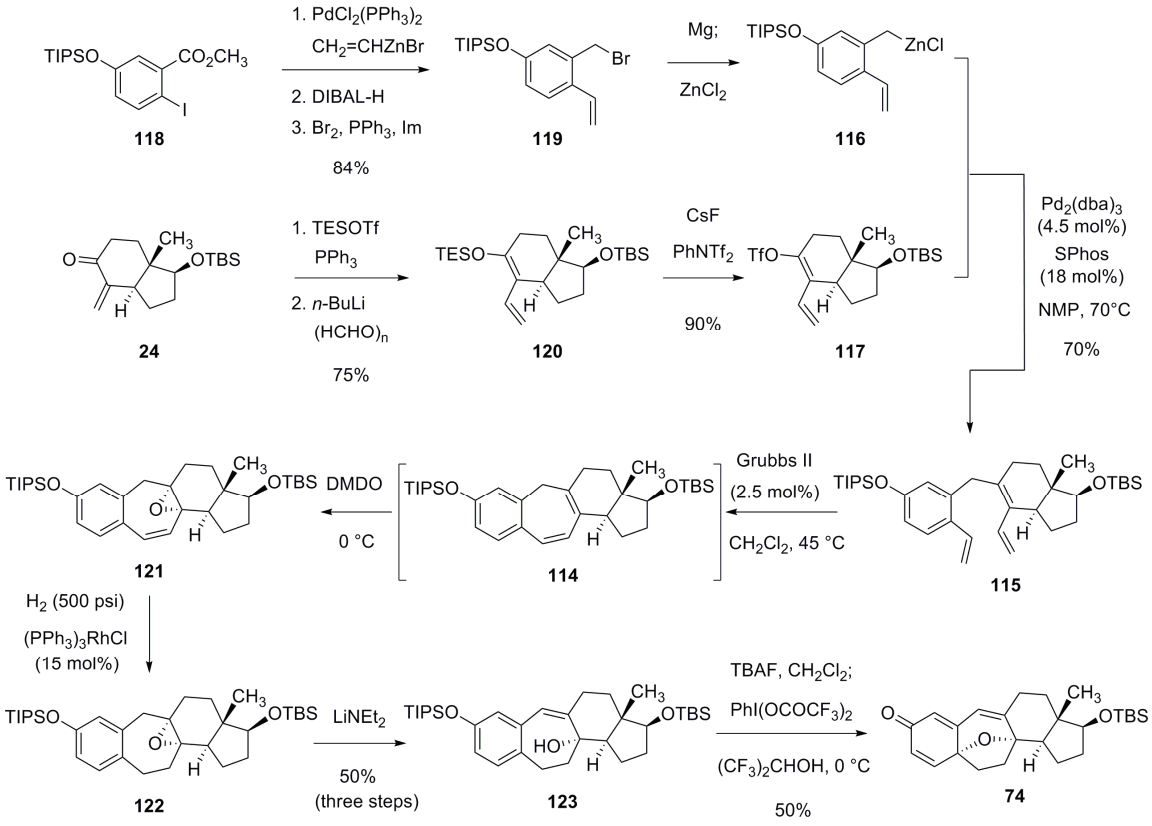
[3] (a) Isaacs, R. C. A.; Digrandi, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1993**, *58*, 3938–3941; (b) Micheli, R. A.; Hojos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Sciamanna, W.; Scott, M. A.; Wehrli, P. A. *J. Org. Chem.* **1975**, *40*, 675–681.

[4] This α-methylene ketone **24** was also used by the Nicolaou group[a,b] and the Sorensen group[c] independently in the synthesis of cortistatins: (a) Nicolaou, K. C.; Sun, Y. P.; Peng, X. S.; Polet, D.; Chen, D. Y. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 7310–7313. (b) Nicolaou, K. C.; Peng, X. S.; Sun, Y. P.; Polet, D.; Zou, B.; Lim, C. S.; Chen, D. Y. K. *J. Am. Chem. Soc.* **2009**, *131*, 10587–10597. (c) Frie, J. L.; Jeffrey, C. S.; Sorensen, E. J. *Org. Lett.* **2009**, *11*, 5394–5397.

[5] (a) Kozikowski, A. P.; Jung, S. H. *J. Org. Chem.* **1986**, *51*, 3400–3402; (b) Evans, D. A.; Hurst, K. M.; Takacs, J. M. *J. Am. Chem. Soc.* **1978**, *100*, 3467–3477.

[6] Mi, Y.; Schreiber, J. V.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 11290–11291.

Scheme 2.1 Synthesis of Cortistatin Core Structure **74**.



benzylzinc reagent **116**) at 70 ºC to afford triene **115** in 70% yield on a 16-g scale.[7] Warming the triene product with the second-generation Grubbs catalyst (0.025 equiv) in dichloromethane at 45 ºC furnished the tetracyclic diene **114**;[8] the crude reaction mixture was diluted with dichloromethane, cooled in an ice-bath and treated with a solution of dimethyldioxirane (DMDO) in acetone,[9] which led to a stereoselective epoxidation of the tetrasubstituted alkene, providing a tetracyclic diene monoepoxide **121**. Without purification, this epoxide was hydrogenated in benzene under 500 psi hydrogen in the

[7] Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871–1876.
[8] Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
[9] Murray, R. W.; Singh, M. *Organic Syntheses;* Wiley & Sons: New York, 1997; Vol. 74, pp 91–100. The procedure was slightly modified and scaled up to produce DMDO solution in acetone (typically 0.06 M) on liter-scale.

presence of Wilkinson's catalyst (0.15 equiv) to afford epoxide **122**. The latter product then underwent selective eliminative opening at C19 benzylic position with lithium diethylamide,[10] furnishing the conjugated allylic alcohol **123** in 50% yield over three steps. Selective removal of the phenolic triisopropylsilyl protective group with tetra-*n*-butylammonium fluoride (TBAF) at 0 ºC was followed by oxidative cyclization of the resulting phenol **113** with [bis(trifluoroacetoxy)-iodo]benzene in a mixture of dichloromethane and hexafluoroisopropanol,[11] providing the cyclohexadienone core structure **74** in 50% yield on a 2-g scale.[12] By applying this optimized procedure, over 10 g of the cyclohexadienone **74** have been prepared to date.

With gram-quantities of cyclohexadienone **74** in hand, the next stage was to functionalize the A ring to prepare the key intermediate **112**. It was found that the disubstituted C3,C4 double bond of **74** could be selectively hydrogenated under 500 psi hydrogen in the presence of Wilkinson's catalyst (0.1 equiv) to provide mono-enone **124** in 80% yield (Scheme 2.2). This enone was converted to an extended silyl enol ether **126** by treating with triethylsilyl trifluoromethanesulfonate (1.5 equiv) in the presence of 2,6-lutidine (2 equiv), which was brominated in the same pot with *N*-bromosuccinimide (NBS, 2 equiv) to afford keto-bromide **125** as a single diastereomer in 75% yield. The exclusive axial bromination selectivity was likely due to a favorable chair-like conformation rather than a twisted-boat-like conformation in the transition state.[13]

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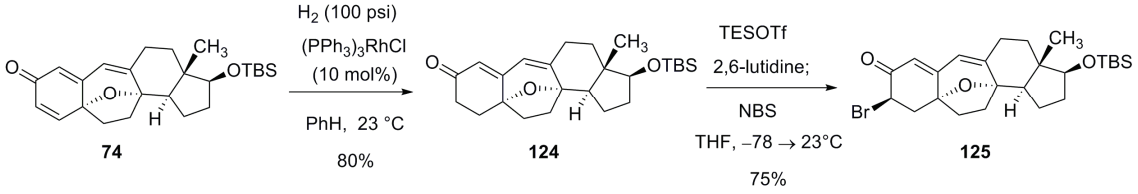
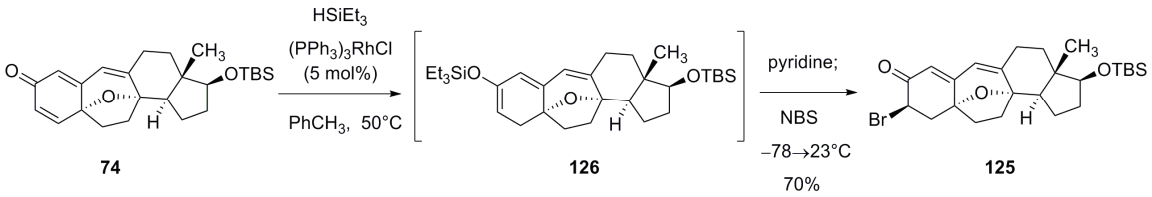
[10] Thummel, R. P.; Rickborn, B. Base *J. Org. Chem.* **1972**, *37*, 3919–3923.
[11] The incorporation of fluorinated solvents improves yields in phenolic oxidations: Kita, Y.; Tohma, H.; Kikuchi, K.; Inagaki, M.; Yakura, T. *J. Org. Chem.* **1991**, *56*, 435–438.
[12] Similar oxidative cylization strategies were also used by the Sarpong group,[a,b] the Danishefsky group,[c] and the Sorensen group[4c] independently in the synthesis of cortistatins, see Chapter 1 for details: (a) Simmons, E. M.; Hardin-Narayan, A. R.; Guo, X.; Sarpong, R. *Tetrahedron*, **2010**, 66, 4696–4700 (b)Simmons, E. M.; Hardin, A. R.; Guo, X.; Sarpong, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 6650–6653.(c) Dai, M. J.; Danishefsky, S. J. *Heterocycles* **2009**, *77*, 157–161.
[13] Kirby, A. J. In *Stereoelectronic Effects*; Oxford University Press Inc., New York, 1996; pp 59–60.

Scheme 2.2 Synthesis of Keto Bromide **74** by Hydrogenation and Bromination.



The knowledge learned in the two-step synthesis of keto bromide **125** informed a more efficient, one-pot hydrosilylation-bromination sequence (Scheme 2.3). After extensive experimentation, it was found that heating cyclohexadienone **74** with triethylsilane (2 equiv) in the presence of Wilkinson's catalyst (0.05 equiv) in toluene at 50 ºC provided the same extended triethylsilyl enol ether intermediate **126**;[14] without isolation, pyridine was added as a co-solvent (14% by volume) followed by *N*-bromosuccinimide (NBS, 2 equiv), affording the (3*R*)-keto bromide **125**, again as a single diastereomer, in 70% yield. In the absence of pyridine, or with lesser quantities of pyridine,[15] the bromination reaction was much less stereoselective, which suggested that Wilkinson's catalyst might not be innocent during the bromination.

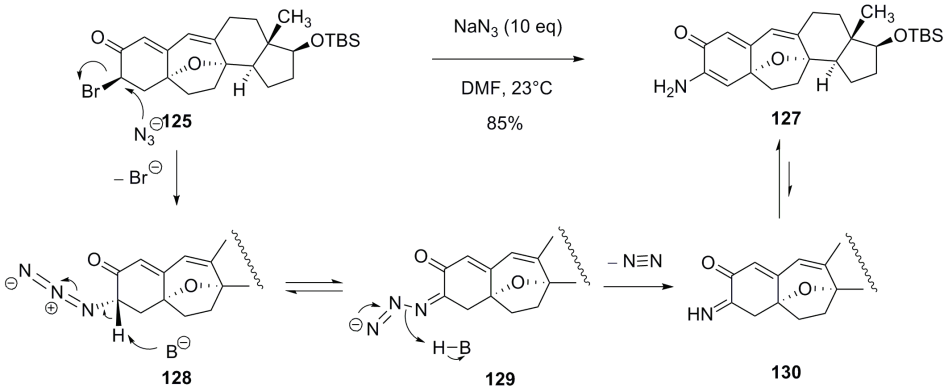
Scheme 2.3 Synthesis of Keto Bromide **125** by a One-pot Hydrosilylation-Bromination.



[14] Kogure, T.; Ojima, I. *Organometallics* **1982**, *1*, 1390–1399.
[15] It is known that pyridine complexed to Wilkinson's catalyst and reduced its hydrogenation ability: Heaton, B.T.; Iggo, J. A.; Jacob, C.; Nadarajah, J.; Fontaine, M. A.; Messere, R.; Noels. A. F. *J. Chem. Soc. Dalton. Trans.* **1994**, 2875–2880.

The keto bromide in **125** was subsequently displaced to introduce a C3 azide as a nitrogen-containing handle. However, when **125** was treated with excess sodium azide (10 equiv) in *N,N*-dimethylformamide at room temperature for 12 h, an unexpected keto enamine product **127** was isolated as the major product (Scheme 2.4).[16] Mechanistically, we speculated that after the initial S_N2 substitution, the α-proton of the keto azide **128** could be deprotonate by the basic azide anion to afford intermediate **129**; a molecule of nitrogen was then released and the resulting imine **130** was isomerized to afford the more stable keto enamine **127**.[17,18]

Scheme 2.4 Unexpected Formation of Keto Enamine **127** from Keto Bromide **125**.

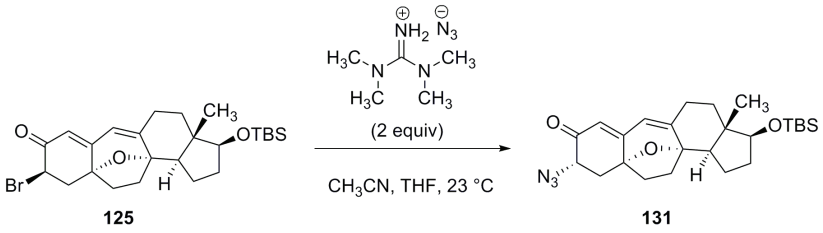


The problem was solved by using a milder organic azide, tetramethylguanidinium azide (TMGA, 2 equiv)[19,20] which is soluble in a number of organic solvents, and the reaction could be conducted in a much less polar solvent system (a mixture of 2:1

[16] When 1 equiv of sodium azide was used in the same reaction condition for 12 h, an approximately 1:1:1 mixture of starting keto bromide **125**, keto enamine **12**, and desired keto azide **125** was observed.
[17] For a similar reaction mechanism, see: Salunke, D. B.; Hazra, B. G.; Gonnade, R. G.; Bhadbhadeb, M. M.; Pore, V. S. *Tetrahedron* **2005**, *61*, 3605–3612.
[18] In a recent report, Danishefsky and co-workers also observed a similar reaction in their cortistatin synthesis, see: Wang, Z.; Dai, M. J.; Park, P. K.; Danishefsky, S. J. *Tetrahedron* **2011**, *67*, 10249–10260.
[19] Papa, A. J. *J. Org. Chem.* **1966**, *31*, 1426–1427.
[20] For a review article on the use of TMGA, see: Błaszczyk, R. *Synlett* **2008**, 299–300.

acetonitrile and tetrahydrofuran), which we believed to help suppressing the formation of the undesired keto enamine side product. In the optimal conditions, the displacement proceeded within 5 h at room temperature with clean inversion of C3-stereochemistry, providing desired (3*S*)-α-azido ketone **131** as a yellow solid, with less than 5% of keto enamine **127** observed.

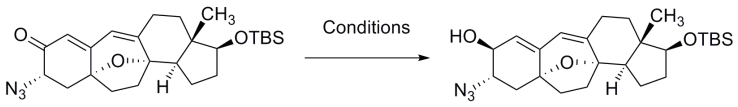
Scheme 2.5 Synthesis of Keto Azide **131** with Tetramethylguanidinium Azide (TMGA).



Without purification, this azido ketone **131** was directly reduced to give the key intermediate azido alcohol **112** (Scheme 2.6). In order to achieve high diastereoselectivity, a number of different conditions were screened. Metal hydride reductions gave modest selectivity in favor of the desired (2*S*)-alcohol (entries 1–3); (*S*)-Corey-Bakshi-Shibata (CBS) catalyst (0.2 equiv) provided mostly (2*R*)-alcohol (entry 4), while (*R*)-CBS with borane dimethyl sulfide complex catalyst afforded almost exclusively (2*S*)-alcohol (>20:1 dr, entry 5).[21] This selectivity is in agreement with Corey's model if considering the azide side as the large group and the diene side as the small group.[21] Despite the great selectivity, reduction by employing borane dimethyl sulfide complex gave only modest yield, most likely due to competing hydroboration on the diene moiety during the transformation. Thus, a more hindered borane source, catecholborane (2 equiv) was used

[21] Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.

Scheme 2.6 Redution of Keto Azide **131** to Key Intermediate **112**.

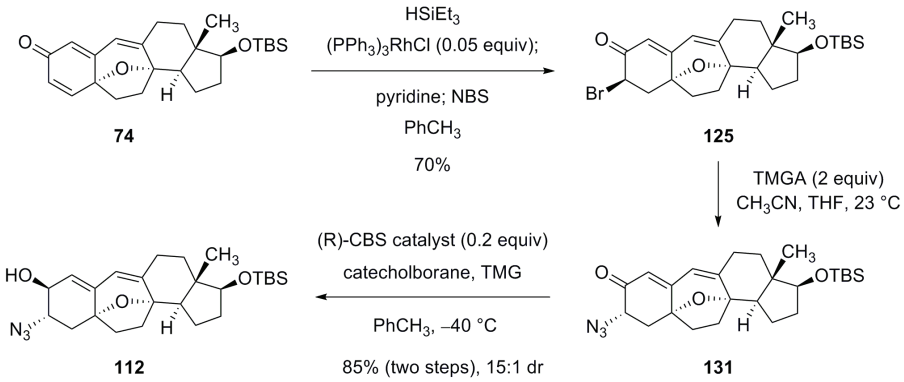


131 **112**

Entry	Reducing conditons	Yield (over two steps)	dr (2*S* : 2*R*)
1	$NaBH_4$, 0 °C	80%	3 : 1
2	$LiAlH(Ot\text{-}Bu)_3$, 0 °C	80%	5 : 1
3	$LiAlH_4$, –78 °C	55%	5.5 : 1
4	(*S*)-CBS, BH_3•SMe_2, 23 °C	50%	1 : 5
5	(*R*)-CBS, BH_3•SMe_2, 23 °C	55%	> 20 : 1
6	(*R*)-CBS, catechol borane, –40 °C	85%	4:1 → 15:1
7	(*R*)-CBS, catechol borane, TMG, –40 °C	85%	15 : 1

at a lower temperature (–40 ºC) in the presence of (*R*)-CBS catalyst (0.2 equiv) and an additive tetramethylguanidine (1 equiv), and the yield was improved to 85% over two steps with a slightly diminished diastereoselectivity (15:1 dr, entry 7). Addition of tetramethylguanidine was found to be beneficial for the reproducibility of the reaction (entry 6); a similar phenomena was observed by Corey and coworkers by using *N,N'*-diethylaniline as an additive in their catecholborane mediated CBS reduction.[22] With this optimized sequence (Scheme 2.7), the key intermediate **112** was prepared on 1.0-g batches, and over 3 g of this azido alcohol has been produced to date.

Scheme 2.7 Optimized Synthesis of Key Intermediate **112** from Cyclohexadienone **74**.

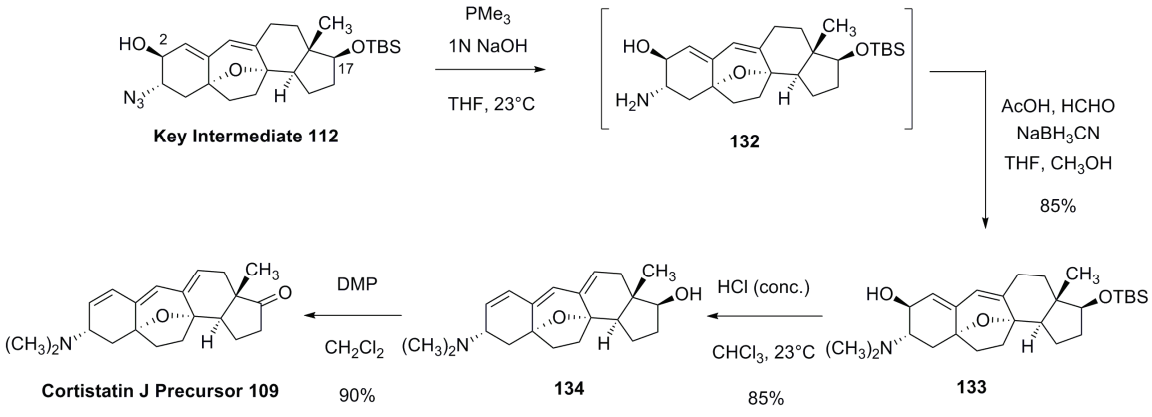


[22] Chein, R. J.; Yeung, Y. Y.; Corey, E. J. *Org. Lett.* **2009**, *11*, 1611–1614.

Synthesis of Cortistatin J, Cortistatin K, and Cortistatin L Precursors

With gram-quantities of the key intermediate **112** in hand, the next step was to convert it to different cortistatin 17-keto precursors **108**, **109**, **110** and **111** (Figure 2.1). In cortistatin J, a triene is present along the northern edge of the ABC-ring (Scheme 2.8). The azide was first reduced under Staudinger reaction conditions with excess trimethylphospine (5 equiv) in a mixture of tetrahydrofuran and 1N aqueous sodium hydroxide solution (4:1) to provide an amino alcohol **132**;[23] without isolation, this amine intermediate was reductively (di)aminated with a large excess of sodium formalin and cyanoborohydride under slightly acidic condition to afford dimethylamino alcohol **133** in 85% yield. When this amino-alcohol product was treated with concentrated hydrochloride acid in chloroform at 23 ºC, a 1,6-elemination reaction took place cleanly and the C17 *tert*-butyldemethylsilyl ether was also cleaved at the same time, giving triene **134** with a cortistatin J skeleton in good yield. Finally, the resulting C17 alcohol was

Scheme 2.8 Synthesis of a Cortistatin J Precursor **109**.

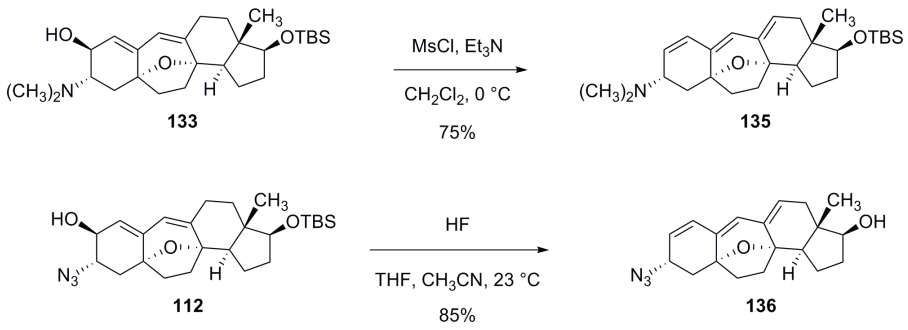


[23] Aqueous sodium hydroxide solution was found to be necessary for the Staudinger reduction; using water instead led to no desired product.

oxidized with Dess−Martin periodinane[24] to provide a 17-keto cortistatin J precursor **109** in 90% yield (three steps from key intermediate **112** in 65% overall yield).

Interestingly, it was found that amino acohol **132** also underwent a facile 1,6-elemination upon mesylation in the presence of triethylamine to give triene **135** in good yields (Scheme 2.9), which served as a good evidence for the biosynthetic origins of cortistatin J.[1, 25] Meanwhile, my coworker, Dr. Ge Zou found that treating the key intermediate **112** directly with hydrofluoric acid also led to a 1,6-elemination-desilylation product **136**, which was used in the synthesis of a cortistatin J-based affinity probe (see Chapter 3 for details).

Scheme 2.9 Base and Acid Induced 1,6-Elemination to Give Cortistatin J Frameworks.

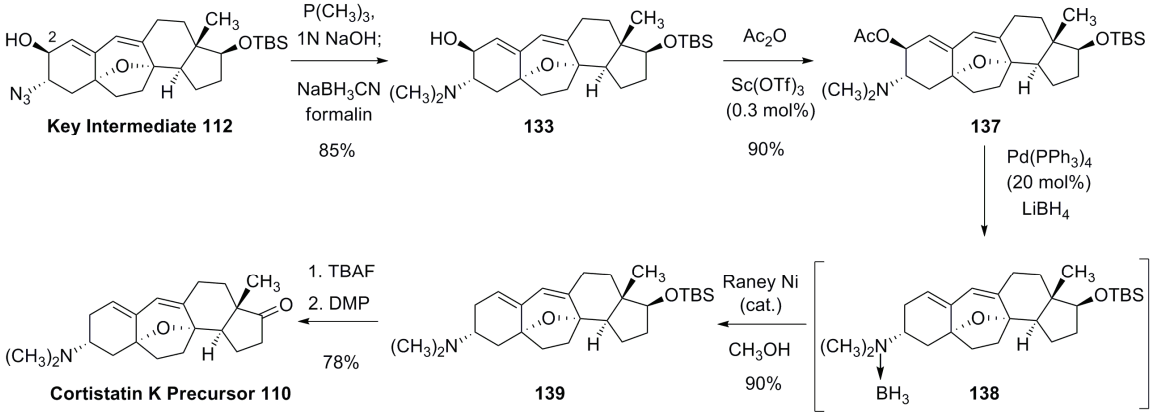


In the synthesis of a cortistatin K precursor **110**, the C2 allylic alcohol needs to be removed (Scheme 2.10). Key intermediate **112** was converted to dimethylamino alcohol **133** via the same Staudinger-reductive-(di)amination sequence as described in the cortistatin J series. Initial attempts to remove the hydroxyl group under radical

[24] Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4158.
[25] Flyer, A. N.; Si, C.; Myers, A. G. *Nature Chemistry* **2010**, *2*, 886–892.

deoxygenation,[26] ionic hydrogenation,[27] or nickel boride reduction conditions[28] were not successful, thus reduction via palladium π-allyl complex was next pursued. After acetylation of C2 alcohol with excess acetic anhydride in the presence of scandium triflate (0.003 equiv),[29] regioselective reductive cleavage of the allylic C-O bond of acetate **137** was achieved by employing tetrakis(triphenylphosphine)palladium (0.2 equiv) and excess lithium borohydride (2 equiv) at 23 ºC,[30] producing an unexpected dimethylamino-borane complex **138** as a non-polar, chromatography-stable white solid. Decomplexation was achieved in the same pot by using a known protocol with catalytic amount of Raney nickel in methanol,[31] affording the free amine **139**, also as a white solid, in excellent yield. Subsequently, silyl ether cleavage with tetra-*n*-butylammonium fluoride (TBAF) and Dess−Martin periodinane oxidation completed the route to the cortistatin K precursor **110** (five steps from key intermediate **112** in 54% overall yield).

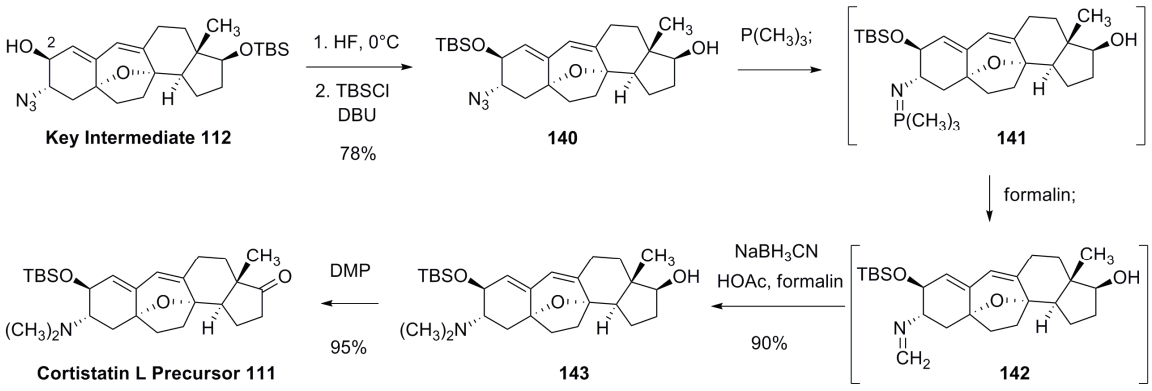
Scheme 2.10 Synthesis of a Cortistatin K Precursor **110**.



[26] For a general review of radical deoxygenation, see: Hartwig, W. *Tetrahedron* **1983**, *39*, 2609–2645.
[27] (a) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633–651;(b) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773–775.
[28] He, Y.; Pan, X.; Wang, S.; Zhao, H. *Synth. Commun.* **1989**, *19*, 3051–3054.
[29] Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1985***, 117,* 4413–4414.
[30] Hutchins, R. O.; Learn, K.; Fulton, R. P. *Tetrahedron Lett.* **1980**, *21*, 27–30.
[31] Couturier, M.; Tucker, J. L.; Andresen, B. M.; Dube, P.; Negri, J. T. *Org. Lett.* **2001**, *3*, 465–467.

In the synthesis of a cortistatin L precursor **111** (in corporation with Dr. Alec Flyer, Scheme 2.11), hydrofluoric acid promoted C17 desilylation of **112** was followed by selective protection of its less hindered C2 hydroxyl group by using a combination of *tert*-butyldimethylsilyl chloride and 1,8-diaza-bicycloundec-7-ene (DBU) in tetrahydrofuan[32] to provide intermediate **140** in 78% yield over two steps. The C3 azide group was then reduced to amine. However, standard Staudinger conditions proved to be slow and low-yielding, presumably due to the bulk of the adjacent *tert*-butyl-dimethylsilyl ether. After much experimentation, a novel procedure was developed, in which azide **140** was first stirred with excess anhydrous trimethylphosphine (5 equiv) for 20 h to allow its complete conversion to an iminophosphorane intermediate **141**; then formalin was added to react with **141** in an *aza*-Wittig manner;[33] and the resulting imine **142** was reductive (di)aminated with excess sodium cyanoborohydride in the presence of formalin under acidic conditions, furnishing dimethylamine **143** in 90% yield. Finally, the C17 hydroxyl group of **143** was oxidized with Dess−Martin periodinane to afford cortistatin L precursor **111** (four steps from key intermediate **112** in 67% overall yield).

Scheme 2.11 Synthesis of a Cortistatin L Precursor **112**.

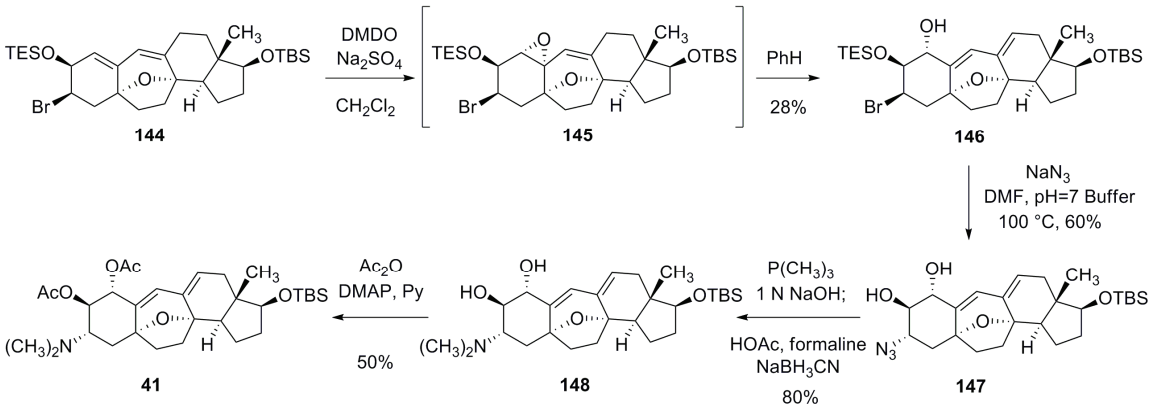


[32] Moon, S. S.; Stuhmiller, L. M.; McMorris, T. C. *J. Org. Chem.* **1989**, *54*, 26–28.
[33] Treatment of the iminophosphorane **141** with water led to low yield of the desired product.

A Formal Synthesis of Cortistatin A and Synthesis of a Cortistatin A Precursor

Dr. Alec Flyer observed that treating diene **144** (prepared in two steps from keto bromide **125**) with dimethyldioxirane (DMDO) afforded a highly sensitive epoxide **145** as the primary product, which upon standing in benzene solution underwent spontaneous 1,4-eliminative opening to form dienyl alcohol **146** (Scheme 2.12).

Scheme 2.12 A Formal Synthesis of a Cortistatin A.



From **146**, a three-step sequence was developed to synthesize Shair's intermediate **41**.[34] The C-3 secondary bromide in **146** was displaced with a large excess sodium azide (50 equiv) in a 4:1 mixture of *N,N*-dimethylformamide and pH=7 aqueous potassium phosphate buffer solution at 100 ºC, in which the pH=7 buffer was found to significantly reduce the amount of the bromide elimination side product; the C-2 triethylsilyl ether was also cleaved in the same operation, affording azido trans-diol **147** in 60% yield. Subsequently, a Staudinger-reductive-(di)aminaition sequence similar to the one used in

[34] Lee, H. M.; Nieto-Oberhuber, C.; Shair, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 16864–16866.

the cortistatins J and K series afforded dimethylamino trans-diol **148** in 80% yield, which was bis-acetylated with excess acetic anhydride (10 equiv) and 4-dimethylaminopyridine (DMAP, 2 equiv) in pyridine as a solvent to provid the Shair's intermediate **41** in modest yield.

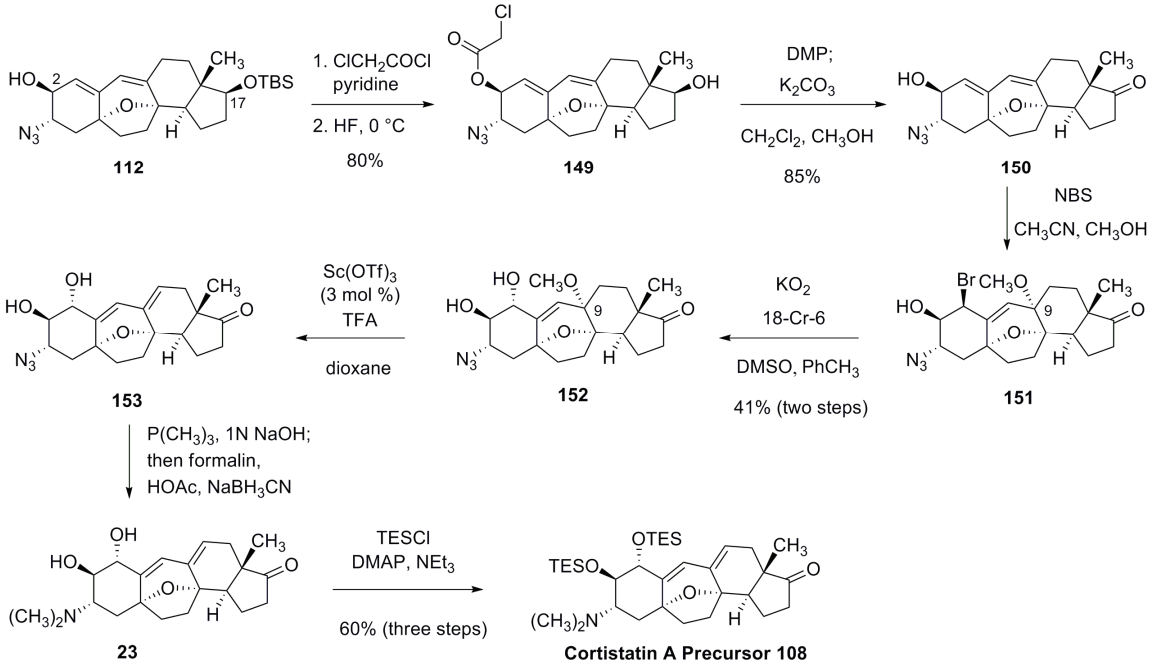
Despite the successful preparation of acetate **41**, the lengthy and low-yielding sequence prevented us from large-scale production of the cortistatin A precursor. Therefore, a more efficient route was developed (Scheme 2.13). Dr. Alec Flyer was able to convert key intermediate **112** to azido *trans*-diol **153** in six steps. The C2 hydroxyl group of key intermediate **112** was temporarily protected as a chloroacetate, and C17 *tert*-butyldimethylsilyl ether was cleavage with hydrofluoric acid at 0 ºC to provide intermediate **149** in 80% yield over two steps. This C17 alcohol was oxidized with Dess-Martin periodinane, and in the same pot, the C2 chloroacetate was removed by addition of methanol and potassium carbonate, to afford ketone **150** in 85% yield. Addition of *N*-bromosuccinimide (1.02 equiv) to a solution of **150** in a 3:1 mixture of acetonitrile and methanol led to a stereoselective, *trans*-diaxial 1,4-bromoetherification of the conjugated diene to provide C1 axial, allylic bromide product **151**.[35] Without purification, this bromide was displaced with potassium superoxide in the presence of 18-crown-6,[36] affording *trans*-diol methyl ether **152** in 41% yield over two steps. The C9 axial methyl ether in **152** then underwent 1,2-elimination by exposure to a mixture of scandium triflate (0.03 equiv) and excess trifluoroacetic acid (9.4 equiv) in dioxane, furnishing azido *trans*-diol **153**.

---

[35] (a) Deagostino, A.; Tivola, P. B.; Prandi, C.; Venturello, P. *Synlett* **1999**, 1841–1843; (b) Fraser-Reid. B; Radatus, B. *J. Chem. Soc. Chem. Comm.* **1970**, 779–780.

[36] (a) San Filippo, J.; Chern, C. I. ; Valentine, J. S. *J. Org. Chem.* **1975**, *40*, 1678–1680; (b) Corey, E. J.; Nicolaou, K. C.; Shibasaki, M.; Machida, Y.; Shiner, C. S. *Tetrahedron Lett.* **1975**, *37*, 3183–3186.

Scheme 2.13 Synthesis of a Cortistatin A Precursor **108**.

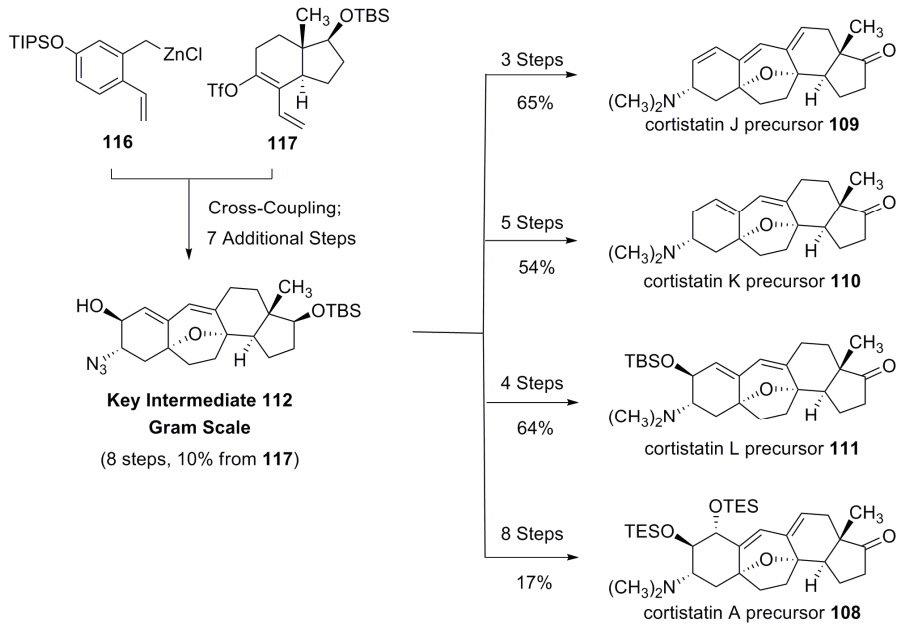


The azido diol **153** was subsequently transformed to a cortistatin A precursor **108**. A previously described Staudinger-reductive-(di)aminaition sequence in which the azide **153** was first reduced by exposure to excess trimethylphospine (5 equiv) in a 2:1mixture of tetrahydrofuran and 1N aqueous sodium hydroxide solution, then (di)aminated in the same pot with a large excess of sodium cyanoborohydride and formalin under slightly acidic environment afforded dimethylamino diol **23**. The two hydroxyl groups of **23** were subsequently protected with chlorotriethylsilane (6 equiv) in the presence of triethylamine (12 equiv) and 4-dimethylaminopyridine (DMAP, 2 equiv) in *N,N*-dimethylformamide, providing a protected 17-keto cortistatin A precursor **108** in 60% yield over three steps on a 75-mg scale (8 steps from key intermediate **112** with 17% overall yield).

Conclusion

In summary, we have developed a robust route to produce the key intermediate azido alchol **112** on gram scale by an efficient assembly of a readily available benzyl zinc reagent **116** and an enol triflate reagent **117** in eight steps (including Negishi cross-coupling, Ring-closing-metathesis-then-epoxidation, hydrogenation, epoxide-opening, oxidative-dearomatization, hydrosilylation-bromination, nucleophilic-displacement, and CBS-reduction) (Figure 2.2). This key intermediate was subsequently transformed to cortistatin J precursor **109**, cortistatin K precursor **110**, cortistatin L precursor **111**, and cortistatin A precursor **108** in three to eight steps. These precursors represent each of the four natural cortistatin ABC-ring substitution patterns, which were elaborated to final cortistatin natural products as described in Chapter 3.

Figure 2.2 Summary of the Syntheses of Cortistatin Precursors from Key Intermediate **112**.



Experimental Section

General Experimental Procedures. All reactions were performed in round-bottomed flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation (house vacuum, ca. 25–40 Torr) at ambient temperature, unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60 Å pore-size, 230–400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light, then were stained with either an aqueous sulfuric acid solution of ceric ammonium molybdate (CAM) or acidic ethanolic *p*-anisaldehyde solution (*p*-anisaldehyde) then briefly heated on a hot plate. Flash-column chromatography was performed as described by Still et al.,[37] employing silica gel (60 Å, 32–63 μM, standard grade, Dynamic Adsorbents, Inc.).

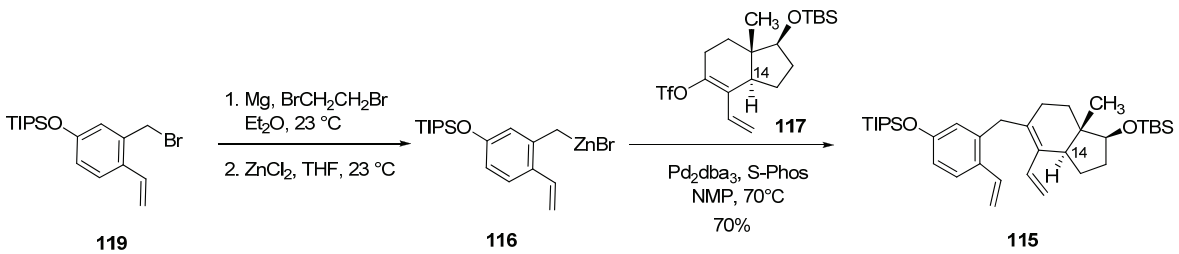
Materials. Commercial solvents and reagents were used as received with the following exceptions. Tetrahydrofuran, dichloromethane, benzene, toluene, dioxane, and ether were purified by the method of Pangborn et al.[38] *N*-Bromosuccinimide was recrystallized from water. The molarity of *n*-butyllithium solutions was determined by titration against a standard solution of diphenylacetic acid in tetrahydrofuran (average of three determinations).[39]

---

[37] Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
[38] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.
[39] Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879–1880.

Instrumentation. Proton magnetic resonance (^{1}H NMR) spectra were recorded on Varian INOVA 500 (500 MHz) or 600 (600 MHz) NMR spectrometers at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26; C_6D_5H, δ 7.15). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br = broad, app = apparent), integration, and coupling constant (*J*) in Hertz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on Varian INOVA 500 (126 MHz) NMR spectrometers at 23 °C. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, δ 77.0; C_6D_6, δ 128.0). Infrared (IR) spectra were obtained using a Shimadzu 8400S FT-IR spectrometer and were referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (vs = very strong, s = strong, m = medium, w = weak, br = broad). High-resolution mass spectra were obtained at the Harvard University Mass Spectrometry Facility.

*(For clarity, intermediates that have not been assigned numbers in the text are numbered sequentially in the experimental section beginning with **154**).*



119 **116** **115**

Triene **115**.

Note: Magnesium turnings used in this procedure were washed sequentially with 1 N aqueous hydrochloric acid solution (2 × 10 mL), 0.1 N aqueous hydrochloric acid solution (10 mL), water (6 × 10 mL), ethanol (3 × 10 mL), then ether (3 × 10 mL). The washed turnings were dried under high vacuum for 12 h prior to use.

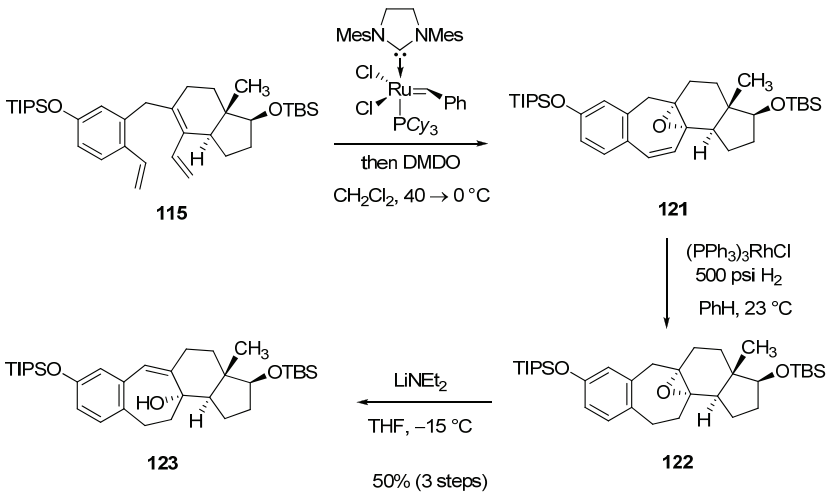
To a flame-dried, 250-mL flask fitted with a reflux condenser and a stirring bar were added magnesium turnings (14.3 g, 587 mmol, 15 equiv) followed by ether (50 mL). The reaction flask was placed in a water bath at 23 ºC. 1,2-dibromoethane (4.05 mL, 47.0 mmol, 1.2 equiv) was added dropwise over a period of 10 min. After 30 min, visible gas evolution had ceased, and a solution of benzyl bromide **119** (17.4 g, 47.0 mmol, 1.2 equiv) in ether (30 mL) was added. After 30 min, the dark green reaction mixture was transferred via cannula to a flask containing a solution of zinc chloride (6.41 g, 47.0 mmol, 1.2 equiv) in tetrahydrofuran (60 mL). The transfer was quantitated with tetrahydrofuran (2 × 10 mL). The resulting cloudy white mixture was allowed to stir at 23 ºC for 40 min. To a separate flame-dried, 1-L flask was added enol triflate **117** (17.3 g, 39.2 mmol, 1 equiv)[40] and *N*-methyl-2-pyrrolidinone (160 mL). The resulting solution was degassed by sparging for 20 min with a slow stream of argon gas through a 20-gauge

[40] Used as a 10:1 mixture of diastereomers (epimeric at C14) carried from α-methylene ketone **24**; the major diastereomer is depicted in the equation above. The minor diastereomer was separated after the Negishi coupling.

stainless steel needle. Tris(dibenzylideneacetone)dipalladium (1.62 g, 1.76 mmol, 0.045 equiv) and 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (2.90 g, 7.05 mmol, 0.18 equiv) were added in sequence. After 10 min, the organozinc reagent prepared in the paragraph above was transferred to the reaction flask via cannula. The resulting cloudy orange suspension was sparged for 20 min with a slow stream of argon gas through a 20-gauge stainless steel needle. The flask was capped with a glass stopper under argon and the stopped flask was sealed with Teflon® tape and then Parafilm®. After sealing, the reaction flask was placed in an oil bath preheated to 70 ºC. After 20 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. The reaction mixture was partitioned between aqueous hydrochloric acid solution (1.0 N, 400 mL) and ether (1.5 L). The layers were separated. The aqueous layer was extracted with ether (2 × 250 mL). The organic layers were combined. The combined solution was washed sequentially with saturated aqueous sodium bicarbonate solution (400 mL), water (400 mL), then saturated aqueous sodium chloride solution (400 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was filtered through silica (hexanes initially, grading to 10:1 hexanes–ether) and the filtrate was concentrated. The residue was purified by flash-column chromatography (hexanes initially, grading to 20:1 hexanes–ether) to furnish a single diastereomer of coupling product **115** as a pale yellow oil (16.0 g, 70%).

^{1}H NMR:	7.35 (dd, 1H, J = 8.3, 2.5 Hz), 6.89 (dd, 1H, J = 17.3,
(500 MHz, $CDCl_3$)	11.0 Hz), 6.70 (dd, 1H, J = 8.5, 2.7 Hz), 6.61 (d, 1H, J =
	2.4 Hz), 6.45 (dd, 1H, J = 17.6, 11.2 Hz), 5.51 (dd, 1H,

	J = 17.6, 1.5 Hz), 5.15 (dd, 1H, J = 11.2, 1.5 Hz), 5.09–5.01 (m, 2H), 3.66 (app t, 1H, J = 8.1 Hz), 3.54 (d, 1H, J = 15.7 Hz), 3.42 (d, 1H, J = 15.6 Hz), 2.31–2.23 (m, 1H), 2.08–1.96 (m, 3H), 1.94–1.85 (m, 1H), 1.69 (ddd, 1H, J = 12.5, 6.3, 1.7 Hz), 1.59–1.52 (m, 1H), 1.49 (dd, 1H, J = 12.2, 5.4 Hz), 1.28–1.16 (m, 4H), 1.07 (d, 18H, J = 7.3 Hz), 0.87 (s, 9H), 0.74 (s, 3H), 0.01 (s, 3H), 0.01 (s, 3H).
^{13}C NMR : (126 MHz, $CDCl_3$)	155.9, 139.2, 134.5, 134.2, 133.1, 132.9, 130.0, 126.6, 119.6, 117.9, 115.1, 113.3, 80.2, 44.8, 43.5, 35.8, 33.7, 31.5, 29.1, 25.9, 24.5, 18.1, 18.0, 12.7, 11.1, –4.5, –4.8; FTIR (neat), cm^{-1} 2945 (m), 2891 (m), 1603 (m), 1491 (m), 1258 (s).
FTIR, cm^{-1}: (thin film)	2945 (m), 2891 (m), 1603 (m), 1491 (m), 1258 (s).
HRMS: (ESI)	Calcd for $(C_{36}H_{60}O_2Si_2+H)^+$ 581.4205, Found 581.4183.
TLC (10:1 hexanes–ethyl acetate)	R_f = 0.90 (UV, *p*-anisaldehyde)



Allylic Alcohol **123**.

Note: Dichloromethane used in this procedure was degassed just prior to use by sparging for 20 min with a slow stream of argon gas through a 20-gauge stainless steel needle.

To a flame-dried, 250-mL flask fitted with a reflux condenser and a stirring bar were added sequentially coupling product **115** (11.2 g, 19.2 mmol, 1 equiv), dichloromethane (96 mL), and the 2nd generation Grubbs catalyst (407 mg, 0.480 mmol, 0.025 equiv). The reaction flask was placed in an oil bath preheated to 40 ºC. After 5 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. The reaction mixture was transferred to a 3-L flask and dichloromethane (1.2 L) was added. The reaction flask was placed in an ice bath, and a solution of dimethyldioxirane in acetone (0.060 M, 480 mL, 28.8 mmol, 1.5 equiv) was then added. After 1 h, hexanes (700 mL) were added and the diluted product solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The black oily residue (vinyl epoxide **121**) was transformed in the following step directly without purification.

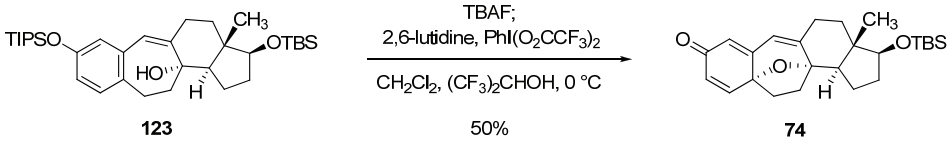
Benzene (5 mL) was added to the oily residue prepared above and volatiles were removed in vacuo through a 16-gauge needle in order to effect azeotropic drying. A

second portion of benzene (5 mL) was added, and the volatiles were again removed. Benzene (64 mL) was added to the concentrate. To the resulting solution was added sodium bicarbonate (2.42 g, 28.8 mmol, 1.5 equiv), followed by Wilkinson's catalyst (2.67 g, 2.88 mmol, 0.15 equiv). The reaction flask was placed in a hydrogenation vessel and the vessel was pressurized to 500 psi with hydrogen. The reaction mixture was stirred vigorously. After 20 h, the pressure was released. Solids were removed by filtration through a pad of Celite, washing with ethyl acetate (3 × 30 mL). The filtrates were combined and the combined organic solution was concentrated. The residue was purified by flash-column chromatography on triethylamine-deactivated silica gel (20:1 hexanes–ethyl acetate initially, grading to 10:1 hexanes–ethyl acetate) to furnish epoxide **122** as a yellow oil (7.67 g, >80% purity by ^{1}H NMR analysis).

A solution of *n*-butyllithium in hexanes (2.50 M, 10.7 mL, 26.8 mmol, 2 equiv) was added dropwise to a solution of diethylamine (3.48 mL, 33.6 mmol, 2.5 equiv) in tetrahydrofuran (60 mL) at –78 ºC. After 15 min, the cooling bath was exchanged for an ice bath and the reaction flask was allowed to warm to 0 ºC. After 15 min, the ice-cold solution was transferred by cannula to a solution of epoxide **122** (7.67 g, 13.4 mmol, 1 equiv) in tetrahydrofuran (200 mL) cooled to –15 ºC in an ice-salt bath. After 20 min, saturated aqueous sodium bicarbonate solution (10 mL) was added. The product solution was concentrated to remove the bulk of solvent. The concentrate was partitioned between water (100 mL) and 1:1 ether–hexanes (300 mL). The layers were separated. The aqueous layer was extracted with ether (2 × 50 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (100 mL) and the washed solution was dried over sodium sulfate. The dried

solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on triethylamine-deactivated silica gel (20:1 hexanes–ethyl acetate initially, grading to 10:1 hexanes–ethyl acetate, then 5:1 hexanes–ethyl acetate) to provide allylic alcohol **123** as a pale yellow foam (5.37 g, 50% three).

^{1}H NMR: (500 MHz, $CDCl_3$)	7.00 (d, 1H, *J* = 8.0 Hz), 6.71 (d, 1H, *J* = 2.5 Hz), 6.65 (dd, 1H, *J* = 8.0, 2.5 Hz), 6.31 (s, 1H), 3.66 (app t, 1H, *J* = 8.6 Hz), 2.84–2.68 (m, 3H), 2.44–2.35 (m, 1H), 2.19–2.11 (m, 1H), 2.07 (s, 1H), 2.04–1.96 (m, 2H), 1.96–1.89 (m, 1H), 1.70–1.59 (m, 3H), 1.58–1.50 (m, 1H), 1.48–1.38 (m, 1H), 1.29–1.19 (m, 3H), 1.09 (d, 18H, *J* = 7.6 Hz), 0.87 (s, 9H), 0.73 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H).
^{13}C NMR : (126 MHz, $CDCl_3$)	154.4, 145.7, 137.4, 133.7, 129.8, 127.4, 121.8, 118.2, 82.5, 74.9, 52.8, 42.6, 39.4, 36.3, 31.2, 30.8, 29.6, 25.8, 19.9, 18.0, 17.9, 13.8, 12.6, –4.4, –4.8.
FTIR, cm^{-1}: (thin film)	3414 (br), 2949 (s), 2866 (m), 1462 (m), 1281 (s).
HRMS: (ESI)	Calcd for $(C_{34}H_{58}O_3Si_2+Na)^+$ 593.3817 Found 593.3803
TLC (5:1 hexanes–ethyl acetate)	R_f = 0.38 (UV, *p*-anisaldehyde)

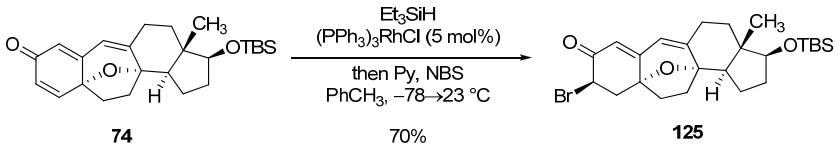


Cyclohexatrienone **74**.

A solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (1.0 M, 10.3 mL, 10.3 mmol, 1.1 equiv) was added to an ice-cooled solution of allylic alcohol **123** (5.33 g, 9.33 mmol, 1 equiv) in dichloromethane (75 mL). After 15 min, 1,1,1,3,3,3-hexafluoro-2-propanol (50 mL) was added, followed by 2,6-lutidine (4.35 mL, 37.4 mmol, 4 equiv). A solution of [bis(trifluoroacetoxy)iodo]benzene (7.23 g, 16.8 mmol, 1.8 equiv) in dichloromethane (25 mL) was then added by cannula over 10 min, forming a bright red solution. After 30 min, the bright red reaction mixture was concentrated to remove the bulk of solvent. The residue was partitioned between aqueous hydrochloric acid solution (0.5 N, 50 mL) and ethyl acetate (300 mL). The layers were separated. The aqueous layer was extracted with ether (3 × 70 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (70 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on triethylamine-deactivated silica gel (15:1 hexanes–ethyl acetate initially, grading to 7:1 hexanes–ethyl acetate, then 5:1 hexanes–ethyl acetate, two purifications were necessary to obtain product of >95% purity by ^{1}H NMR analysis), affording cyclohexatrienone **74** as a pale yellow solid (1.98 g, 50%).

^{1}H NMR: 6.43 (d, 1H, J = 9.8 Hz), 6.20 (dd, 1H, J = 10.0, 1.7 Hz),

(500 MHz, $CDCl_3$)	5.93 (s, 1H), 5.49 (d, 1H, J = 2.0 Hz), 3.37 (app t, 1H, J = 8.1 Hz), 2.12–2.02 (m, 1H), 1.93 (dd, 1H, J = 17.0, 3.4 Hz), 1.85 (dd, 1H, J = 11.5, 7.5 Hz), 1.80–1.72 (m, 1H), 1.71–1.60 (m, 3H), 1.57 (ddd, 1H, J = 13.1, 6.3, 1.6 Hz), 1.51–1.41 (m, 3H), 1.20–1.13 (m, 1H), 0.98 (s, 9H), 0.89 (app td, 1H, J = 12.9, 4.9 Hz), 0.70 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H).	
^{13}C NMR :	185.7, 157.4, 154.4, 146.6, 129.9, 119.8, 119.1, 86.2,	
(126 MHz, $CDCl_3$)	81.7, 75.3, 47.7, 43.9, 37.3, 36.2, 30.8, 29.1, 28.9, 26.0, 19.7, 18.3, 11.0, –4.3, –4.7.	
FTIR, cm^{-1}:	2955 (s), 2857 (m), 1661 (vs), 1611 (s), 1354 (m), 1257	
(thin film)	(s).	
HRMS:	Calcd for $(C_{25}H_{36}O_3Si+H)^+$	413.2507
(ESI)	Found	413.2505
TLC	R_f = 0.40 (UV, *p*-anisaldehyde)	
(4:1 hexanes–ethyl acetate)		



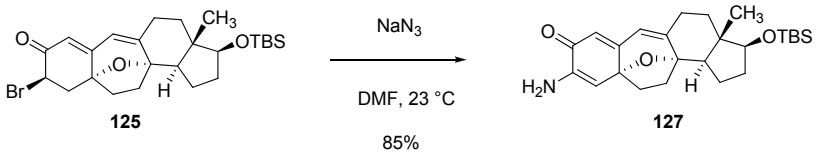
Bromo Ketone **125**.

Note: Toluene used in this procedure was degassed using the freeze-pump-thaw method (4 iterations). Triethylsilane was filtered through a pipette packed with neutral alumina just prior to use.

To a flame-dried flask charged with cyclohexatrienone **74** (1.96 g, 4.74 mmol, 1 equiv) was added toluene (2 mL). Volatiles were removed in vacuo through a 20-gauge needle in order to effect azeotropic drying. A second portion of toluene (2 mL) was added, and the volatiles were again removed. Triethylsilane (1.52 mL, 9.50 mmol, 2 equiv) was added to the concentrate followed by a solution of Wilkinson's catalyst (220 mg, 0.238 mmol, 0.05 equiv) in toluene (96 mL), the latter added via cannula. The reaction flask was then placed in an oil bath preheated to 50 ºC. After 4 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. Pyridine (16 mL) was added. After 12 h, the reaction flask was cooled to −78 ºC and a solution of *N*-bromosuccinimide (1.69 g, 9.48 mmol, 2.0 equiv) in tetrahydrofuran (10 mL) was added by cannula. After 1 h, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 0.5 h, the reaction mixture was partitioned between saturated aqueous sodium thiosulfate solution (50 mL) and ethyl acetate (250 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (80 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified

by flash-column chromatography on silica gel (20:1 hexanes–ethyl acetate initially, grading to 8:1 hexanes–ethyl acetate) to provide diastereomerically pure bromo ketone **125** as a white solid (1.63 g, 70%).

^{1}H NMR: (500 MHz, $CDCl_3$)	5.92 (d, 1H, *J* = 2.3 Hz), 5.61 (s, 1H), 4.59 (ddd, 1H, *J* = 4.6, 2.3, 1.1 Hz), 3.64 (app t, 1H, *J* = 8.2 Hz), 2.93 (dd, 1H, *J* = 15.0, 4.7 Hz), 2.59–2.36 (m, 3H), 2.31 (ddd, 1H, *J* = 13.4, 9.4, 6.0 Hz), 2.09 (app td, 1H, *J* = 11.4, 5.8 Hz), 2.04–1.94 (m, 1H), 1.90 (dd, 1H, *J* = 10.6, 8.8 Hz), 1.86–1.73 (m, 2H), 1.69–1.48 (m, 4H), 1.23 (ddd, 1H, *J* = 12.9, 4.5 Hz), 0.89 (s, 9H), 0.84 (s, 3H), 0.02 (s, 6H).	
^{13}C NMR : (126 MHz, $CDCl_3$)	191.2, 160.3, 158.9, 119.4, 116.5, 83.4, 81.4, 76.0, 47.7, 44.7, 43.9, 41.1, 37.2, 36.1, 30.6, 29.9, 29.3, 25.8, 19.4, 18.1, 10.9, –4.4, –4.9.	
FTIR, cm^{-1}: (thin film)	2953 (m), 2856 (m), 1668 (s), 1618 (s), 1250 (m).	
HRMS: (ESI)	Calcd for $(C_{25}H_{37}BrO_3Si+H)^+$	493.1768
	Found	493.1768
TLC (5:1 hexanes–ethyl acetate)	R_f = 0.50 (UV, *p*-anisaldehyde)	

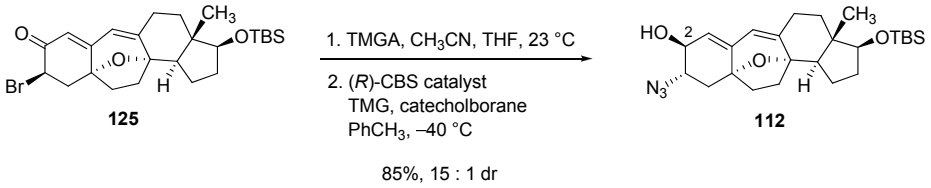


Keto Enamine **127**.

Sodium azide (26.0 mg, 0.406 mmol, 10 equiv) was added to a solution of bromo ketone **125** (20.0 mg, 0.041 mmol, 1 equiv) in *N,N*-dimethylformamide (1.0 mL) at 23 ºC. After 12 h, the reaction mixture was partitioned between half saturated aqueous sodium chloride solution (10 mL) and ether (15 mL). The layers were separated. The aqueous layer was extracted with ether (3 × 10 mL). The organic layers were combined. The combined solution was washed with water (10 mL) and then saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (10:1 hexanes–ethyl acetate initially, grading to 4:1 hexanes–ethyl acetate) to provide keto enamine **127** as a yellow solid (14.9 mg, 85%).

^{1}H NMR: (500 MHz, C_6D_6) 5.94 (s, 1H), 5.51 (s, 1H), 5.36 (s, 1H), 3.48 (br. s., 2H), 3.38 (t, 1H, *J* = 8.1 Hz), 2.11 (app td, 1H, *J* = 15.5, 3.0 Hz), 1.96 (dd, 1H, *J* = 16.9, 4.6 Hz), 1.90 (dd, 1H, *J* = 12.2, 7.0 Hz), 1.84 (ddd, 1H, *J* = 14.0, 10.5, 2.6 Hz), 1.80–1.75 (m, 1H), 1.75–1.67 (m, 3H), 1.62–1.55 (m, 2H), 1.52 (dd, 1H, *J* = 12.0, 4.9 Hz), 1.48–1.42 (m, 1H), 1.17 (ddd, 1H, *J* = 12.5, 9.2, 2.7 Hz), 0.98 (s, 9H), 0.93

	(app td, 1H, J = 12.9, 4.8 Hz), 0.74 (s, 3H), 0.01 (d, 6H, J = 2.5 Hz);	
^{13}C NMR : (126 MHz, C_6D_6)	181.5, 158.8, 154.1, 138.7, 118.6, 116.7, 111.4, 84.3, 80.8, 75.4, 46.9, 42.9, 36.5, 35.2, 29.8, 28.1, 27.0, 25.0, 18.7, 17.3, 10.1, -5.3, -5.7;	
FTIR, cm^{-1}: (thin film)	3468 (br), 3362 (br), 2955 (s), 2926 (s), 2857 (m), 1641 (m), 1616 (s), 1464 (m), 1250 (m).	
HRMS: (ESI)	Calcd for $(C_{25}H_{38}NO_3Si+H)^+$	428.2615
	Found	428.2631
TLC (2:1 hexanes–ethyl acetate)	R_f = 0.47 (UV, *p*-anisaldehyde)	



Azido Alcohol **112**.

Tetramethylguanidinium azide (960 mg, 6.08 mmol, 2 equiv) was added to a solution of bromo ketone **125** (1.50 g, 3.04 mmol, 1 equiv) in a mixture of acetonitrile (60 mL) and tetrahydrofuran (30 mL). After 12 h, the solution was concentrated to remove the bulk of solvent. Ethyl acetate (100 mL) and ether (50 mL) were added. Solids were removed by filtration, washing with ether (3 × 50 mL). The filtrates were combined and the combined solution was concentrated.

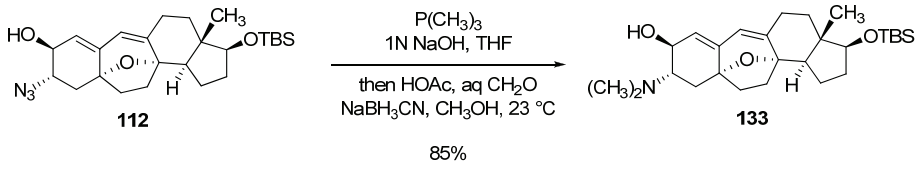
Toluene (2 mL) was added, and volatiles were removed in vacuo through a 20-gauge needle in order to effect azeotropic drying. A second portion of toluene (2 mL) was added, and the volatiles were again removed. Toluene (60 mL) was added to the concentrate. Tetramethylguanidine (382 µl, 3.04 mmol, 1 equiv) and a solution of (*R*)-tetrahydro-1-methyl-3,3,-diphenyl-1*H*,3*H*-pyrrolo[1,2-c][1,3,2]oxazaborole catalyst in toluene (1.0 M, 608 µl, 0.608 mmol, 0.2 equiv) were added in sequence. The reaction flask was then cooled to –40 ºC. A solution of catecholborane in toluene (1.0 M, 6.08 mL, 6.08 mmol, 2 equiv) was added dropwise over 5 min. After 2 h, excess catecholborane was quenched by the addition of methanol (2 mL). The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was then partitioned between aqueous sodium hydroxide solution (1.0 N, 15 mL) and ethyl acetate (120 mL). The layers were separated. The organic layer was washed with aqueous sodium hydroxide solution (1.0 N, 3 × 15 mL). The aqueous layers were combined. The

combined aqueous solution was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (9:1 hexanes–ether, grading to 3:1 hexanes–ether) to furnish azido alcohol **112** as a white foam (1.18 g, 85%, a 15:1 mixture of diastereomers).[41]

^{1}H NMR: (500 MHz, $CDCl_3$)	5.69 (d, 1H, *J* = 2.3 Hz), 5.14 (d, 1H, *J* = 2.3 Hz), 4.24 (app td, 1H, *J* = 5.4, 2.5 Hz), 3.60 (app t, 1H, *J* = 8.5 Hz), 3.49 (ddd, 1H, *J* = 12.7, 8.6, 3.9 Hz), 2.52–2.37 (m, 1H), 2.34–2.23 (m, 1H), 2.18 (d, 1H, *J* = 5.0 Hz), 2.13–2.00 (m, 4H), 2.00–1.89 (m, 2H), 1.89–1.77 (m, 2H), 1.73 (ddd, 1H, *J* = 12.5, 5.6, 1.6 Hz), 1.68–1.55 (m, 2H), 1.55–1.43 (m, 1H), 1.13 (app td, 1H, *J* = 13.2, 4.8 Hz), 0.87 (s, 9H), 0.79 (s, 3H), 0.01 (s, 6H).
^{13}C NMR : (126 MHz, $CDCl_3$)	148.6, 142.0, 118.5, 118.4, 83.9, 81.6, 78.0, 72.4, 63.4, 47.8, 43.9, 38.3, 38.3, 36.3, 32.5, 30.5, 28.6, 25.8, 19.6, 18.0, 10.8, –4.5, –4.9.

[41] The product obtained in this procedure is a 15:1 mixture of diastereomers (epimeric at C2); the major diastereomer is depicted in the equation above. The minor diastereomer was removed at different points in the syntheses of the cortistatins, as detailed in the procedures that follow.

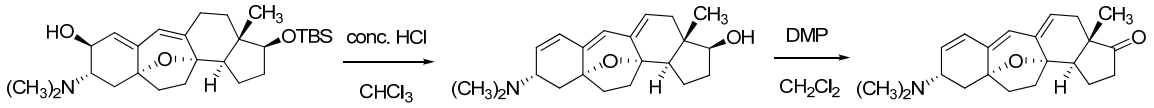
FTIR, cm^{-1}:	3431 (br), 2953 (m), 2857 (m), 2102 (vs), 1251 (s).	
(thin film)		
HRMS:	Calcd for $(C_{25}H_{39}N_3O_3Si+Na)^+$	480.2653
(ESI)	Found	480.2651.
TLC	R_f = 0.34 (UV, *p*-anisaldehyde)	
(3:1 hexanes–ethyl acetate)		



Dimethylamino Alcohol **133** (Cortistatin J and K Series).

A solution of azido alcohol **112**[41] (80 mg, 175 μmol, 1 equiv) in a mixture of tetrahydrofuran (5 mL) and aqueous sodium hydroxide solution (1.0 N, 1 mL) was degassed by sparging for 20 min with a slow stream of argon gas through a 20-gauge stainless steel needle. To the degassed solution was added a solution of trimethylphosphine in tetrahydrofuran (1.0 M, 525 μL, 525 μmol, 3 equiv). After 2 h, methanol (6 mL) was added, followed by aqueous hydrochloric acid solution (1.0 N, 1 mL) then acetic acid (200 μL, 3.50 mmol, 20 equiv). Formalin (37 wt %, 710 μL, 8.75 mmol, 50 equiv) and a solution of sodium cyanoborohydride (110 mg, 1.75 mmol, 10 equiv) in methanol (1 mL) were added in sequence. After 1 h, the reaction mixture was concentrated to remove the bulk of solvent. The concentrate was partitioned between aqueous sodium hydroxide solution (1.0 N, 20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (4 × 20 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (15 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 5:1 ethyl acetate–methanol, then 1:1 ethyl acetate–methanol) to furnish diastereomerically pure dimethylamino alcohol **133** (cortistatin J and K series) as a white solid (68 mg, 85%).

^{1}H NMR: (500 MHz, $CDCl_3$)	5.70 (d, 1H, *J* = 2.1 Hz), 5.29 (d, 1H, *J* = 1.5 Hz), 4.22 (d, 1H, *J* = 9.2 Hz), 3.59 (app t, 1H, *J* = 8.5 Hz), 3.48 (br s, 1H), 2.59 (ddd, 1H, *J* = 12.5, 9.4, 2.5 Hz), 2.49–2.37 (m, 1H), 2.30 (s, 6H), 2.29–2.20 (m, 1H), 2.12–1.89 (m, 3H), 1.89–1.75 (m, 5H), 1.71 (dd, 1H, *J* = 12.5, 4.0 Hz), 1.67–1.54 (m, 2H), 1.54–1.43 (m, 1H), 1.12 (app td, 1H, *J* = 13.0, 4.6 Hz), 0.87 (s, 9H), 0.79 (s, 3H), 0.01 (s, 6H).	
^{13}C NMR : (126 MHz, $CDCl_3$)	δ147.3, 141.0, 119.9, 119.1, 83.7, 81.6, 79.5, 67.6, 66.2, 48.0, 43.9, 40.4, 38.4, 36.4, 32.5, 30.6, 30.3, 28.6, 25.8, 19.6, 18.0, 10.9, –4.5, –4.9.	
FTIR, cm^{-1}: (thin film)	3431 (br), 2955 (s), 2859 (m), 1462 (m), 1250 (s), 1134 (s), 1044 (s).	
HRMS: (ESI)	Calcd for $(C_{27}H_{45}NO_3Si+H)^+$	460.3242
	Found	460.3259.
TLC (methanol)	R_f = 0.32 (UV, *p*-anisaldehyde)	



Dimethylamino Ketone **109** (Cortistatin J Series).

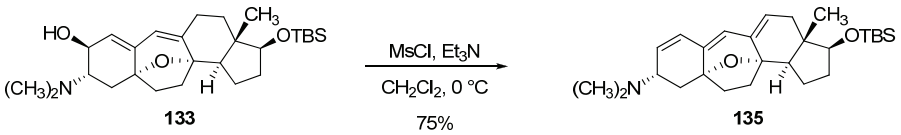
Concentrated aqueous hydrochloric acid solution (37 wt %, 2.15 mL, 26.1 mmol, 300 equiv) was added to a solution of dimethylamino alcohol (cortistatin J and K series) **133** (40 mg, 87.0 μmol, 1 equiv) in chloroform (4 mL). The resulting biphasic mixture was stirred vigorously. After 20 min, the reaction flask was placed in an ice bath and saturated aqueous sodium carbonate solution (20 mL) was added dropwise over 10 min (CAUTION: gas evolution). The layers were separated. The aqueous layer was extracted with dichloromethane (4 × 20 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (15 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 5:1 ethyl acetate–methanol, then 1:1 ethyl acetate–methanol) to furnish trienyl alcohol **134** (cortistatin J series) as a white solid (25 mg, 87%) which was transformed in the following step directly.

Dess-Martin periodinane (97 mg, 229 μmol, 3 equiv) was added to an ice-cooled solution of the trienyl alcohol **134** prepared above (25 mg, 76.3 μmol, 1 equiv) in dichloromethane (3.5 mL). After 10 min, the ice bath was removed and the reaction flask was allowed to warm to 23 ºC. After 2 h, ethyl acetate (10 mL) was added, followed by a mixture of water (4 mL), saturated aqueous sodium thiosulfate solution (4 mL), and saturated aqueous sodium bicarbonate solution (2 mL). The resulting biphasic mixture

was stirred vigorously until both layers were clear. The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 5:1 ethyl acetate–methanol, then 1:1 ethyl acetate–methanol) to furnish dimethylamino ketone **109** (cortistatin J series) as a white solid (22 mg, 77% over two steps).

^{1}H NMR: (500 MHz, $CDCl_3$)	6.09 (dd, 1H, *J* = 9.7, 2.6 Hz), 5.83 (d, 1H, *J* = 9.7 Hz), 5.82 (s, 1H), 5.43 (dd, 1H, *J* = 5.0, 3.0 Hz), 3.44 (d, 1H, *J* = 11.0 Hz), 2.52 (dd, 1H, *J* = 18.8, 8.7 Hz), 2.44 (dd, 1H, *J* = 12.6, 5.5 Hz), 2.31 (s, 6H), 2.29–2.26 (m, 1H), 2.26–2.19 (m, 3H), 2.19–2.14 (m, 1H), 2.08 (ddd, 1H, *J* = 11.0, 9.0, 2.2 Hz), 1.99 (app t, 1H, *J* = 12.0 Hz), 1.95–1.87 (m, 2H), 1.85–1.77 (m, 1H), 1.76–1.69 (m, 1H), 0.95 (s, 3H).
^{13}C NMR : (126 MHz, $CDCl_3$)	220.5, 141.1, 140.1, 132.5, 127.2, 121.0, 120.8, 81.9, 79.2, 60.4, 47.9, 47.3, 40.5, 38.0, 35.9, 34.2, 31.4, 31.0, 18.9, 17.1.

FTIR, cm^{-1}: (thin film)	2967 (s), 2864 (m), 1744 (vs), 1454 (m), 1153 (m), 1078 (m).	
HRMS: (ESI)	Calcd for $(C_{21}H_{27}NO_2+H)^+$	326.2115
	Ffound	326.2119.
TLC (methanol)	R_f = 0.32 (UV, *p*-anisaldehyde)	



Triene **135**.

Methanesulfonyl chloride (3.3 μL, 41.3 μmol, 2 equiv) was added to an ice-cooled solution of the dimethylamino alcohol **133** (9.5 mg, 20.7 μmol, 1 equiv) and triethylamine (9.0 μL, 62.0 μmol, 3 equiv) in dichloromethane (0.50 mL). After 40 min, saturated aqueous sodium bicarbonate solution (0.20 mL) was added. The reaction mixture was then partitioned between saturated aqueous sodium bicarbonate solution (10 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 ethyl acetate–methanol initially, grading to 5:1 ethyl acetate–methanol, then 2:1 ethyl acetate–methanol) to afford triene **135** as a pale yellow solid (6.8 mg, 75%).

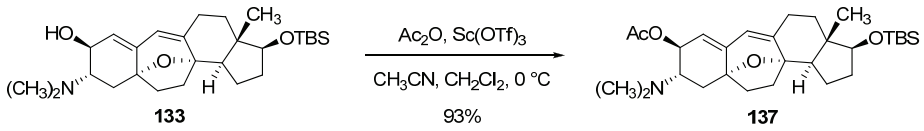
^{1}H NMR: (500 MHz, $CDCl_3$) 6.10 (d, 1H, J = 10.0 Hz), 5.83 (s, 1H), 5.78 (d, 1H, J = 9.6 Hz), 5.49–5.32 (m, 1H), 3.77 (app t, 1H, J = 8.7 Hz), 3.47 (br d, 1H, J = 10.0 Hz), 2.33 (s, 6H), 2.25 (app t, 1H, J = 12.0 Hz), 2.21–2.09 (m, 2H), 2.09–1.92 (m, 4H), 1.88 (dd, 1H, J = 11.0, 4.6 Hz), 1.83–1.60 (m, 4H), 1.60–1.47 (m, 1H), 0.89 (s, 9H), 0.77 (s, 3H), 0.03 (s,

6H).

^{13}C NMR :	141.0, 139.4, 131.3, 127.7, 122.7, 121.5, 82.4, 81.7,
(126 MHz, $CDCl_3$)	78.8, 60.5, 46.4, 43.5, 40.4, 39.6, 38.1, 30.9, 30.7, 30.6,
	25.8, 19.5, 18.1, 13.4, –4.4, –4.8.
FTIR, cm^{-1}:	2957 (s), 2859 (m), 1620 (s), 1572 (s), 1514 (m), 1462
(thin film)	(m), 1248 (s).

HRMS:	Calcd for $(C_{27}H_{43}NO_2Si+H)^+$	442.3136
(ESI)	Found	442.3139

TLC	R_f = 0.45 (UV, *p*-anisaldehyde)
(methanol)	

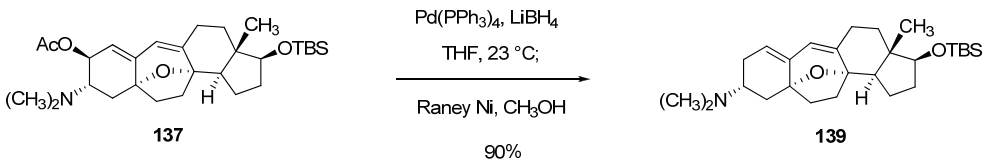


Acetate **137** (Cortistatin K Series).

Scandium trifluoromethanesulfonate (2.68 mg, 5.44 μmol, 0.05 equiv) was added to an ice-cooled solution of dimethylamino alcohol **133** (cortistatin J and K series) (50 mg, 109 μmol, 1 equiv) and acetic anhydride (205 μL, 2.175 μmol, 20.0 equiv) in a mixture of acetonitrile (1.0 mL) and dichloromethane (1.0 mL). After 1 h, saturated aqueous sodium bicarbonate solution (200 μL) was added and the resulting biphasic mixture was concentrated to remove the bulk of solvent. The concentrate was partitioned between ethyl acetate (30 mL) and saturated aqueous potassium carbonate solution (10 mL). The layers were separated. The organic layer was washed with saturated aqueous potassium carbonate solution (10 mL). The aqueous layers were combined. The combined aqueous solution was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated to provide acetate **137** (cortistatin K series) as an off-white solid (51 mg, 93%).

^{1}H NMR: (500 MHz, $CDCl_3$) 5.67 (d, 1H, *J* = 2.0 Hz), 5.55 (d, 1H, *J* = 8.8 Hz), 5.09 (d, 1H, *J* = 2.4 Hz), 3.60 (app t, 1H, *J* = 8.3 Hz), 2.89 (ddd, 1H, *J* = 12.7, 9.3, 3.4 Hz), 2.49–2.39 (m, 1H), 2.29 (s, 6H), 2.30 (s, 6H), 2.30–2.25 (m, 1H), 2.07 (s, 3H), 2.06–1.99 (m, 2H), 1.98–1.79 (m, 6H), 1.75–1.69

	(m, 1H), 1.68–1.55 (m, 2H), 1.54–1.45 (m, 1H), 1.14 (app td, 1H, J = 13.2, 4.9 Hz), 0.90–0.85 (m, 9H), 0.79 (s, 3H), 0.01 (s, 6H).	
^{13}C NMR : (126 MHz, $CDCl_3$)	171.0, 148.4, 143.1, 118.6, 116.7, 83.5, 81.6, 78.8, 70.2, 62.4, 47.9, 43.9, 40.6, 37.6, 36.3, 32.6, 32.3, 30.5, 28.5, 25.8, 21.6, 19.6, 18.0, 10.9, –4.5, –4.9.	
FTIR, cm^{-1}: (thin film)	2953 (m), 2858 (m), 1734 (m), 1369 (m), 1238 (s).	
HRMS: (ESI)	Calcd for $(C_{29}H_{47}NO_4Si+H)^+$	502.3347
	Found	502.3327
TLC (methanol)	R_f = 0.69 (UV, *p*-anisaldehyde)	



137 **139**

tert-Butyldimethylsilyl Ether **139** (Cortistatin K Series)**.**

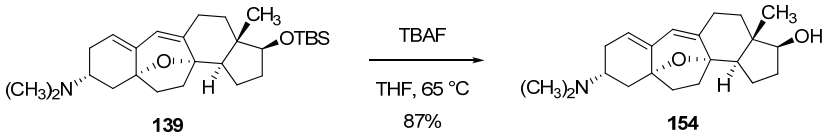
Note: Tetrahydrofuran used in this procedure was degassed by sparging for 20 min with a slow stream of argon gas through a 22-gauge stainless steel needle prior to use. Raney nickel was prepared according to the procedure of Baran and coworkers.[42]

A solution of lithium borohydride in tetrahydrofuran (1.0 M, 1.0 mL, 1.0 mmol, 10 equiv) was added dropwise to a solution of acetate **133** (cortistatin K series) (50 mg, 99.6 μmol, 1 equiv) and tetrakis(triphenylphosphine)palladium(0) (23 mg, 19.9 μmol, 0.2 equiv) in tetrahydrofuran (4 mL). After 1 h, methanol (10 mL) was added, followed by a slurry of Raney nickel in water (4 drops, ca. 0.2 mL). After 16 h, the reaction mixture was filtered through a pad of Celite, washing with methanol (3 × 10 mL). The filtrates were combined and the combined organic solution was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 5:1 ethyl acetate–methanol, then 1:1 ethyl acetate–methanol) to furnish *tert*-butyldimethylsilyl ether **139** (cortistatin K series) as a pale yellow solid (39 mg, 90%).

^{1}H NMR:	5.69 (d, 1H, J = 2.0 Hz), 5.26–5.20 (m, 1H), 3.59 (app t,
(500 MHz, $CDCl_3$)	1H, J = 8.3 Hz), 2.77–2.65 (m, 1H), 2.52–2.37 (m, 1H),
	2.33 (s, 6H), 2.30 (s, 1H), 2.27–2.20 (m, 2H), 2.19–2.07
	(m, 1H), 2.07–1.89 (m, 4H), 1.89–1.76 (m, 3H), 1.76–

[42] Shi, J.; Shigehisa, H.; Guerrero, C. A.; Shenvi, R. A.; Li, C. C.; Baran, P. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 4328–4331.

	1.68 (m, 1H), 1.68–1.54 (m, 2H), 1.54–1.42 (m, 1H), 1.12 (app td, 1H, J = 13.1, 4.6 Hz), 0.88 (s, 9H), 0.79 (s, 3H), 0.01 (s, 6H).	
^{13}C NMR : (126 MHz, $CDCl_3$)	145.4, 140.2, 119.4, 117.4, 83.3, 81.7, 79.2, 58.8, 48.0, 43.9, 41.1, 38.8, 36.6, 36.5, 33.0, 30.6, 28.5, 28.2, 25.8, 19.7, 18.1, 10.9, –4.5, –4.9.	
FTIR, cm^{-1}: (thin film)	2955 (s), 2657 (m), 1738 (m), 1472 (m), 1252 (s).	
HRMS: (ESI)	Calcd for $(C_{27}H_{45}NO_2Si+H)^+$	444.3292
	Ffound	444.3293.
TLC (methanol)	R_f = 0.31 (UV, p-anisaldehyde)	

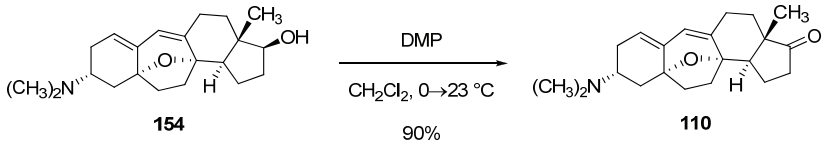


Dimethylamino Alcohol **154** (Cortistatin K Series).

A solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (1.0 M, 250 µL, 250 µmol, 3 equiv) was added to a solution of *tert*-butyldimethylsilyl ether **139** (cortistatin K series) (37 mg, 83.4 µmol, 1 equiv) in tetrahydrofuran (2.1 mL). The reaction flask was placed in an oil bath preheated to 65 ºC. After 3 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. The reaction mixture was then concentrated to remove the bulk of solvent. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 5:1 ethyl acetate–methanol, then 2:1 ethyl acetate–methanol) to furnish dimethylamino alcohol **154** (cortistatin K series) as a white solid (24 mg, 87%).

^{1}H NMR: (400 MHz, $CDCl_3$)	5.70 (d, 1H, *J* = 1.8 Hz), 5.29–5.15 (m, 1H), 3.70 (app t, 1H, *J* = 8.6 Hz), 2.79–2.62 (m, 1H), 2.45 (app t, 1H, *J* = 13.5 Hz), 2.32 (s, 6H), 2.31–2.22 (m, 2H), 2.20–2.07 (m, 2H), 2.06–1.93 (m, 4H), 1.93–1.74 (m, 5H), 1.74–1.44 (m, 3H), 1.21 (ddd, 1H, *J* = 13.0, 4.5 Hz), 0.85 (s, 3H).
^{13}C NMR : (126 MHz, $CDCl_3$)	145.0, 140.1, 119.6, 117.4, 83.1, 81.7, 79.2, 58.7, 48.4, 43.5, 40.8, 38.8, 36.4, 36.1, 33.1, 30.1, 28.4, 27.9, 19.6, 10.7.

FTIR, cm^{-1}: (thin film)	3443 (br), 2955 (s), 2860 (m), 1738 (m), 1462 (m), 1254 (s).	
HRMS: (ESI)	Calcd for $(C_{21}H_{31}NO_2+H)^+$	330.2428
	Found	330.2438
TLC (methanol)	R_f = 0.30 (UV, *p*-anisaldehyde)	

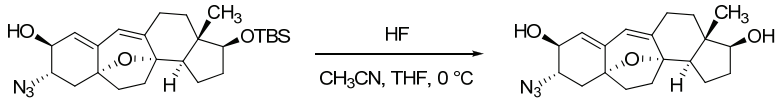


Dimethylamino Ketone **110** (Cortistatin K Series).

Dess-Martin periodinane (77 mg, 183 μmol, 3 equiv) was added to an ice-cooled solution of dimethylamino alcohol **154** (cortistatin K series) (20 mg, 61 μmol, 1 equiv) in dichloromethane (4 mL). After 10 min, the ice bath was removed and the reaction flask was allowed to warm to 23 ºC. After 2 h, ethyl acetate (10 mL) was added, followed by a mixture of water (4 mL), saturated aqueous sodium thiosulfate solution (4 mL), and saturated aqueous sodium bicarbonate solution (2 mL). The resulting biphasic mixture was stirred vigorously until both layers were clear and colorless. The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 5:1 ethyl acetate–methanol, then 2:1 ethyl acetate–methanol) to furnish dimethylamino ketone **110** (cortistatin K series) as a pale yellow solid (18 mg, 90%).

^{1}H NMR: (500 MHz, $CDCl_3$) 5.74 (d, 1H, J = 2.4 Hz), 5.34–5.27 (m, 1H), 2.66 (br s, 1H), 2.51 (dd, 1H, J = 19.0, 9.0 Hz), 2.53–2.43 (m, 1H), 2.41–2.35 (m, 1H), 2.32 (s, 6H), 2.31–2.23 (m, 1H), 2.23–2.07 (m, 4H), 2.07–1.95 (m, 3H), 1.95–1.78 (m,

	5H), 1.39 (app td, 1H, J = 13.3, 5.1 Hz), 0.96 (s, 3H).	
^{13}C NMR : (126 MHz, $CDCl_3$)	219.8, 143.8, 139.8, 120.4, 118.3, 82.8, 79.5, 58.7, 49.5, 48.1, 41.1, 38.8, 36.6, 35.9, 34.3, 31.3, 28.1, 27.8, 18.8, 14.0.	
FTIR, cm^{-1}: (thin film)	2955 (s), 2857 (m), 1740 (vs), 1472 (m), 1252 (s).	
HRMS: (ESI)	Calcd for $(C_{21}H_{29}NO_2+H)^+$	328.2271
	Found	328.2273.
TLC (methanol)	R_f = 0.30 (UV, *p*-anisaldehyde)	



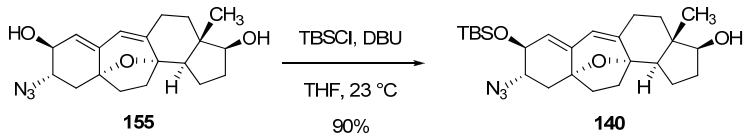
112 **155**

Dienyl Diol **155** (Cortistatin L Series).

Concentrated aqueous hydrofluoric acid solution (48 wt %, 573 μL, 15.9 mmol, 152 equiv) was added dropwise to a polypropylene vessel containing an ice-cooled solution of azido alcohol **112**[41] (48 mg, 105 μmol, 1 equiv) in a mixture of tetrahydrofuran (0.9 mL) and acetonitrile (1.8 mL). After 3 h, the product solution was poured into water (30 mL) containing dipotassium hydrogen phosphate (10 g). The reaction vessel was rinsed with ethyl acetate (40 mL) and the rinse was transferred to the product mixture. The resulting biphasic mixture was stirred vigorously, then was transferred to a separatory funnel. The layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 20 mL). The organic layers were combined. The combined solution was washed sequentially with saturated aqueous sodium bicarbonate solution (30 mL) then saturated aqueous sodium chloride solution (2 × 30 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (initially 20:1 benzene–acetone, grading to 10:1 benzene–acetone, then 5:1 benzene–acetone, then 3:1 benzene–acetone) to furnish diastereomerically pure dienyl diol **155** (cortistatin L series) as a white powder (29.5 mg, 82%).

^{1}H NMR:	.71 (d, 1H, J = 2.3 Hz), 5.16 (s, 1H), 4.24 (d, 1H, J = 7.8
(500 MHz, $CDCl_3$)	Hz), 3.71 (dd, 1H, J = 8.7, 8.6 Hz), 3.50 (ddd, 1H, J =

	12.6, 8.5, 3.7 Hz), 2.52–2.40 (m, 1H), 2.32 (ddd, 1H, *J* = 16.5, 4.6, 1.8 Hz), 2.19–2.00 (m, 5H), 2.00–1.84 (m, 3H), 1.80 (ddd, 1H, *J* = 12.4, 5.5, 1.8 Hz), 1.73–1.46 (m, 4H), 1.42 (br s, 1H), 1.22 (ddd, 1H, *J* = 12.8, 12.7, 4.6 Hz), 0.84 (s, 3H).	
^{13}C NMR : (126 MHz, $CDCl_3$)	148.1, 141.8, 118.8, 118.7, 83.6, 81.6, 78.1, 72.3, 63.4, 48.3, 43.5, 38.3, 38.3, 35.9, 32.6, 30.1, 28.5, 19.5, 10.6.	
FTIR, cm^{-1}: (thin film)	3383 (br), 2926 (m), 2100 (vs), 1255 (m).	
HRMS: (ESI)	Calcd for $(C_{19}H_{25}N_3O_3+Na)^+$	366.1788
	Found	366.1790.
TLC (4:1 benzene-acetone)	R_f = 0.28 (UV, *p*-anisaldehyde)	

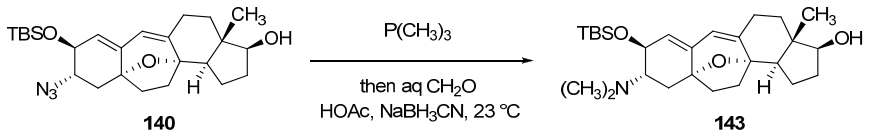


Azido *tert*-Butyldimethylsilyl Ether **140** (Cortistatin L Series).

A freshly-prepared solution of *tert*-butyldimethylsilyl chloride in tetrahydrofuran (1.0 M, 134 μL, 134 μmol, 2 equiv) was added dropwise to a solution of dienyl diol **155** (cortistatin L series) (23 mg, 67.0 μmol, 1 equiv) and 1,8-diazabicyclo[5.4.0]undec-7-ene (100 μL, 670 μmol, 10 equiv) in tetrahydrofuran (0.5 mL). After 24 h, a second portion of *tert*-butyldimethylsilyl chloride solution in tetrahydrofuran (1.0 M, 67 μL, 67 μmol, 1 equiv) was added. After an additional 36 h, the reaction mixture was partitioned between aqueous hydrochloric acid solution (1.0 N, 10 mL) and ethyl acetate (20 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (10:1 hexanes–ethyl acetate initially, grading to 5:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate) to furnish azido *tert*-butyldimethylsilyl ether **140** (cortistatin L series) as a colorless oil (28 mg, 90%).

^{1}H NMR:	5.70 (s, 1H), 5.05 (s, 1H), 4.20 (d, 1H, J = 7.9 Hz), 3.71
(500 MHz, $CDCl_3$)	(app t, 1H, J = 8.6 Hz), 3.46 (ddd, 1H, J = 12.3, 8.1, 4.2
	Hz), 2.53–2.38 (m, 1H), 2.30 (dd, 1H, J = 16.3, 3.7 Hz),

	2.18–2.06 (m, 2H), 2.05–1.96 (m, 2H), 1.96–1.91 (m, 1H), 1.91–1.81 (m, 2H), 1.79 (dd, 1H, J = 12.3, 4.4 Hz), 1.74–1.55 (m, 3H), 1.50 (app tdd, 1H, J = 12.4, 8.3, 3.7 Hz), 1.41–1.34 (m, 1H), 1.21 (app td, 1H, J = 13.0, 4.7 Hz), 0.91 (s, 9H), 0.83 (s, 3H), 0.17 (s, 3H), 0.12 (s, 3H).
^{13}C NMR : (126 MHz, $CDCl_3$)	147.5, 140.7, 120.6, 118.9, 83.5, 81.6, 78.0, 73.3, 63.7, 48.3, 43.5, 38.9, 38.2, 36.0, 32.6, 30.1, 28.5, 25.8, 19.5, 18.0, 10.6, –4.5, –4.8.
FTIR, cm^{-1}: (thin film)	3421 (br), 2955 (s), 2857 (m), 2101 (vs), 1464 (m), 1258 (s).
HRMS: (ESI)	Calcd for $(C_{25}H_{39}N_3O_3Si+Na)^+$ 480.2653 Found 480.2640.
TLC (2:1 hexanes–ethyl acetate)	R_f = 0.39 (UV, *p*-anisaldehyde)

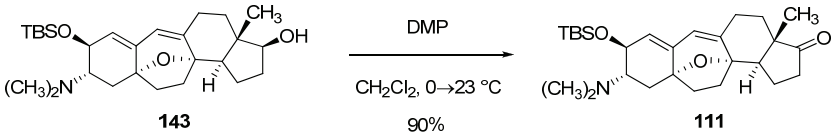


Dimethylamino Alcohol **143** (Cortistatin L Series).

A solution of trimethylphosphine in tetrahydrofuran (1.0 M, 306 μL, 306 μmol, 5 equiv) was added to a solution of azido *tert*-butyldimethylsilyl ether **140** (cortistatin L series) (28 mg, 61.2 μmol, 1 equiv) in tetrahydrofuran (3 mL). After 24 h, formalin (37 wt %, 480 μL, 6.12 mmol, 100 equiv) was added. After 20 h, methanol (3 mL) was added, then acetic acid (70 μL, 1.22 mmol, 20 equiv) and, lastly, a solution of sodium cyanoborohydride (77 mg, 1.22 mmol, 20 equiv) in methanol (1 mL). After 2 h, the reaction mixture was concentrated to remove the bulk of solvent. The concentrate was partitioned between aqueous sodium hydroxide solution (1.0 N, 15 mL) and ethyl acetate (20 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (15 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (66:33:1 hexanes–ethyl acetate–triethylamine initially, grading to 50:49:1 hexanes–ethyl acetate–triethylamine) to provide dimethylamino alcohol **143** (cortistatin L series) as a pale yellow solid (25 mg, 90%).

^{1}H NMR: (500 MHz, $CDCl_3$) 5.70 (d, 1H, J = 2.4 Hz), 5.10 (d, 1H, J = 2.0 Hz), 4.23 (d, 1H, J = 8.3 Hz), 3.71 (app td, 1H, J = 8.4, 5.6 Hz),

	2.67–2.51 (m, 1H), 2.51–2.38 (m, 1H), 2.36–2.28 (m, 1H), 2.27 (s, 6H), 2.18–1.95 (m, 3H), 1.93–1.75 (m, 3H), 1.74–1.59 (m, 2H), 1.58–1.44 (m, 2H), 1.38 (d, 1H, J = 5.4 Hz), 1.25–1.16 (m, 1H), 0.89 (s, 9H), 0.83 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H).
^{13}C NMR : (126 MHz, $CDCl_3$)	146.6, 140.2, 122.9, 119.4, 83.2, 81.7, 79.3, 69.3, 65.7, 48.4, 43.5, 41.0, 37.8, 36.1, 32.7, 32.5, 30.1, 28.4, 26.0, 19.5, 18.3, 10.7, –4.1, –4.7.
FTIR, cm^{-1}: (thin film)	3431 (br), 2930 (s), 2857 (m), 1715 (m), 1472 (m), 1250 (s).
HRMS: (ESI)	Calcd for $(C_{27}H_{45}NO_3Si+H)^+$ 460.3242 Found 460.3250
TLC (50:49:1 hexanes–ethyl acetate–triethylamine)	R_f = 0.19 (UV, *p*-anisaldehyde)

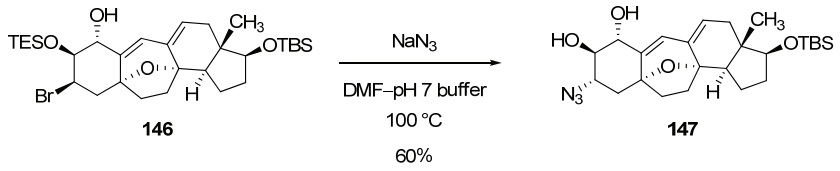


Dimethylamino Ketone **111** (Cortistatin L Series).

Dess-Martin periodinane (69 mg, 163 μmol, 3 equiv) was added to an ice-cooled solution of dimethylamino alcohol **143** (cortistatin L series) (25 mg, 54.4 μmol, 1 equiv) in dichloromethane (2.7 mL). After 10 min, the ice bath was removed and the reaction flask was allowed to warm to 23 ºC. After 2 h, ethyl acetate (10 mL) was added, followed by a mixture of water (4 mL), saturated aqueous sodium thiosulfate solution (4 mL), and saturated aqueous sodium bicarbonate solution (2 mL). The resulting biphasic mixture was stirred vigorously until both layers were clear. The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (66:33:1 hexanes–ethyl acetate–triethylamine initially, grading to 50:49:1 hexanes–ethyl acetate–triethylamine) to furnish dimethylamino ketone **111** (cortistatin L series) as a pale yellow oil (23 mg, 90%).

^{1}H NMR: (500 MHz, $CDCl_3$) 5.73 (d, 1H, J = 2.3 Hz), 5.14 (d, 1H, J = 2.5 Hz), 4.25 (d, 1H, J = 8.2 Hz), 2.66–2.55 (m, 1H), 2.55–2.43 (m, 2H), 2.42–2.33 (m, 1H), 2.28 (s, 6H), 2.24–2.06 (m, 5H), 2.02 (dd, 1H, J = 12.0, 6.5 Hz), 1.96–1.78 (m, 5H), 1.39 (app td, 1H, J = 13.2, 5.2 Hz), 0.97 (s, 3H), 0.89 (s,

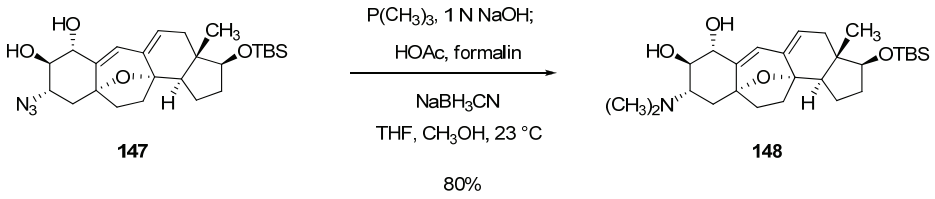
	9H), 0.08 (s, 3H), 0.08 (s, 3H).
^{13}C NMR :	219.7, 145.5, 139.9, 123.6, 120.1, 82.9, 79.6, 69.3, 65.7,
(126 MHz, $CDCl_3$)	49.4, 48.1, 41.0, 37.8, 35.8, 33.9, 32.4, 31.2, 27.8, 26.0,
	18.8, 18.3, 14.0, –4.1, –4.7.
FTIR, cm^{-1}:	2934 (s), 2863 (m), 1740 (vs), 1460 (m), 1248 (s).
(thin film)	
HRMS:	Calcd for $(C_{27}H_{43}NO_3Si+H)^+$ 458.3085
(ESI)	Found 458.3088.
TLC	R_f = 0.24 (UV, *p*-anisaldehyde)
(50:49:1 hexanes–ethyl	
acetate–triethylamine)	



Azido Dienyl Diol **147**.

A solution of bromo dienyl bromide **146** (10 mg, 16.0 μmol, 1 equiv) and sodium azide (52 mg, 800 μmol, 50 equiv) in a mixture of *N,N*-dimethylformamide (0.8 mL) and aqueous potassium phosphate buffer solution (pH 7.0, 0.5 M, 0.20 mL) was degassed by sparging for 10 min with a slow stream of argon gas through a 22-gauge stainless steel needle. The reaction flask was capped with a glass stopper and the stopped flask was sealed with Teflon® tape and then Parafilm®. After sealing, the reaction flask was placed in an oil bath preheated to 100 ºC. After 12 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. The reaction mixture was partitioned between half-saturated aqueous sodium chloride solution (10 mL) and 1:1 hexanes–ethyl acetate (20 mL). The layers were separated. The aqueous layer was extracted with 1:1 hexanes–ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed sequentially with water (10 mL) then saturated aqueous sodium chloride solution (2 × 10 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate initially, grading to 5:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate) to furnish azido dienyl diol **147** as a white solid (4.5 mg, 60%).

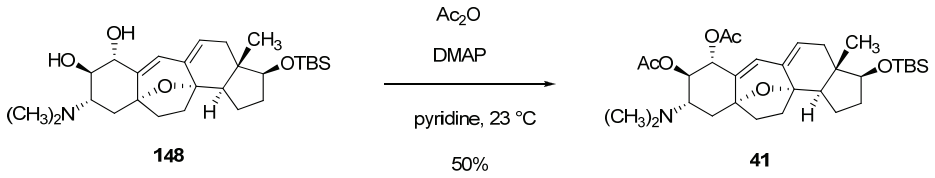
^{1}H NMR:	6.18 (d, 1H, *J* = 2.3 Hz), 5.46 (dd, 1H, *J* = 5.0, 2.3 Hz),
(500 MHz, CDCl3)	4.07 (d, 1H, *J* = 8.2 Hz), 3.76 (app t, 1H, *J* = 8.7 Hz), 3.48–3.26 (m, 2H), 2.25 (app t, 1H, *J* = 11.0 Hz), 2.19–2.06 (m, 3H), 2.06–1.92 (m, 3H), 1.82–1.61 (m, 4H), 1.61–1.44 (m, 2H), 0.88 (s, 9H), 0.74 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H).
^{13}C NMR :	139.0, 138.6, 123.0, 119.9, 82.1, 81.6, 78.4, 78.2, 72.3,
(126 MHz, CDCl3)	60.3, 46.2, 43.4, 39.8, 39.3, 37.5, 30.7, 25.8, 19.4, 18.0, 13.3, –4.4, –4.8.
FTIR, cm^{-1}**:**	3466 (br), 2955 (s), 2857 (m), 2099 (vs), 1472 (m),
(thin film)	1362 (m), 1250 (s).
HRMS:	Calcd for $(C_{25}H_{39}N_3O_4Si+Na)^+$: 496.2602
(ESI)	Found: 496.2619
TLC	R_f= 0.55 (UV, *p*-anisaldehyde)
(1:1 hexanes–ethyl acetate**)**	



Dimethylamino Diol **148**.

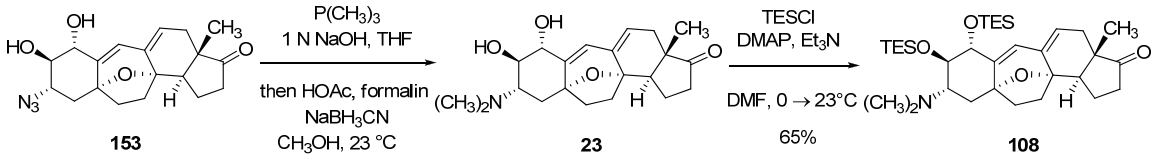
A solution of azido dienyl diol **147** (4.0 mg, 8.44 μmol, 1 equiv) in a mixture of tetrahydrofuran (1.0 mL) and aqueous sodium hydroxide solution (1.0 N, 0.50 mL) was degassed by sparging for 20 min with a slow stream of argon gas through a 22-gauge stainless steel needle. To the degassed solution was added a solution of trimethylphosphine in tetrahydrofuran (1.0 M, 43 μL, 43 μmol, 5 equiv). After 2 h, methanol (2 mL) was added, followed by aqueous hydrochloric acid solution (2.0 N, 0.25 mL) then acetic acid (10 μL, 169 μmol, 20 equiv). To the resulting solution were added sequentially formalin (37 wt %, 70 μL, 844 μmol, 100 equiv) and a solution of sodium cyanoborohydride (11 mg, 169 μmol, 20 equiv) in methanol (0.5 mL). After 1 h, the reaction mixture was concentrated to remove the bulk of solvent. The concentrate was partitioned between aqueous sodium hydroxide solution (1.0 N, 10 mL) and dichloromethane (15 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 ethyl acetate–methanol initially, grading to 1:1 ethyl acetate–methanol) to furnish dimethylamino diol **148** as a white solid (3.2 mg, 80%).

^{1}H NMR: (500 MHz, $CDCl_3$)	6.23 (s, 1H), 5.44 (br s, 1H), 4.09 (d, 1H, J = 9.3 Hz), 3.76 (app t, 1H, J = 8.5 Hz), 3.33 (app t, 1H, J = 9.8 Hz), 2.49 (app t, 1H, J = 10.0 Hz), 2.33 (s, 6H), 2.23 (app t, 1H, J = 11.5 Hz), 2.20–2.07 (m, 2H), 2.04–1.92 (m, 2H), 1.92–1.82 (m, 2H), 1.81–1.64 (m, 3H), 1.64–1.47 (m, 3H), 0.88 (s, 9H), 0.74 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H).
^{13}C NMR : (126 MHz, $CDCl_3$)	139.4, 139.3, 122.2, 119.6, 82.1, 81.7, 79.3, 74.1, 73.7, 62.3, 46.3, 43.4, 40.0, 39.8, 39.3, 30.7, 30.6, 29.2, 25.8, 19.4, 18.1, 13.2, –4.4, –4.8.
FTIR, cm^{-1}: (thin film)	3399 (br), 2955 (s), 2858 (m), 1472 (m), 1387 (m), 1250 (s).
HRMS: (ESI)	Calcd for $(C_{27}H_{45}NO_4Si+H)^+$: 476.3191 Found: 476.3199
TLC (methanol)	R_f = 0.24 (UV, *p*-anisaldehyde)



Dimethylamino Diacetate **41** (Shair's Intermediate).

Acetic anhydride (16 μL, 168 μmol, 40 equiv) was added to a solution of dimethylamino diol **148** (2.0 mg, 4.20 μmol, 1 equiv) and 4-dimethylaminopyridine (2.0 mg, 16.4 μmol, 4 equiv) in pyridine (0.21 mL). After 24 h, the reaction mixture was partitioned between ethyl acetate (20 mL) and saturated aqueous sodium bicarbonate solution (10 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (5:1 hexanes–ethyl acetate initially, grading to 2:1 hexanes–ethyl acetate, then 1:1 hexanes–ethyl acetate) to furnish dimethylamino diacetate **41** as a pale yellow foam (1.2 mg, 50%). The ^{1}H NMR data for **41** was identical to that reported by Shair and coworkers for this compound.[34]



Dimethylamino Ketone **108** (Cortistatin A Series).

A solution of dienyl azido diol (cortistatin A series) **153** (70 mg, 0.196 mmol, 1 equiv) in a mixture of tetrahydrofuran (6 mL) and aqueous sodium hydroxide solution (1.0 N, 3 mL) was degassed by sparging for 20 min with a slow stream of argon gas through a 20-gauge stainless steel needle. To the degassed solution was added a solution of trimethylphosphine in tetrahydrofuran (1.0 M, 588 μL, 0.588 mmol, 3 equiv). After 2 h, methanol (9 mL) was added, followed by aqueous hydrochloric acid solution (3.0 N, 1 mL) then acetic acid (224 μL, 3.92 mmol, 20 equiv). To the resulting solution were added sequentially formalin (37 wt. %, 795 μL, 9.80 mmol, 50 equiv) and a solution of sodium cyanoborohydride (123 mg, 1.96 mmol, 10 equiv) in methanol (1 mL). After 1 h, the reaction mixture was concentrated to remove the bulk of solvent. The concentrate was partitioned between aqueous sodium hydroxide solution (1.0 N, 20 mL) and dichloromethane (40 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (4 × 20 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (30 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (4:1 ethyl acetate-methanol initially, grading to 2:1 ethyl acetate-methanol) to afford dimethylamino keto diol **23** (cortistatin A series) as a white solid (59

mg, 84%). The characteristic data for **23** was identical to that reported by the Baran group and by the Shair group.[34,43]

Chlorotriethylsilane (166 μL, 0.985 mmol, 6 equiv) was added dropwise to an ice-cooled solution of the residue prepared above (59 mg, 0.164 mmol, 1 equiv), triethylamine (275 μL, 1.97 mmol, 12 equiv), and 4-dimethylaminopyridine (40.0 mg, 0.328 mmol, 2 equiv) in *N,N*-dimethylformamide (2.0 mL). After 30 min, the ice bath was removed and the reaction flask was allowed to warm to 23 ºC. After 3 h, the reaction mixture was partitioned between ethyl acetate (30 mL) and a 1:1:1 mixture of water, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution (15 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 15 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (2 × 20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate initially, grading to 4:1 hexanes–ethyl acetate) to afford dimethylamino ketone **108** (cortistatin A series) as a colorless oil (75 mg, 77%).

^{1}H NMR:	6.02 (d, 1H, *J* = 2.0 Hz), 5.38 (dd, 1H, *J* = 4.9, 2.9 Hz),
(500 MHz, $CDCl_3$)	3.99 (d, 1H, *J* = 7.8 Hz), 3.50 (app t, 1H, *J* = 7.6 Hz),
	2.57–2.44 (m, 2H), 2.39 (dd, 1H, *J* = 12.7, 5.4 Hz), 2.22

[43] (a) Shenvi, R. A.; Guerrero, C. A.; Shi, J.; Li, C.-C.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7241–7243;(b) Shi, J.; Manolikakes, G.; Yeh, C.-H.; Guerrero, C. A.; Shenvi, R. A.; Shigehisa, H.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 8014–8027.

	(s, 6H), 2.30–2.17 (m, 5H), 2.16–2.10 (m, 1H), 1.95 (app t, 1H, J = 12.7 Hz), 1.91–1.79 (m, 2H), 1.79–1.60 (m, 2H), 0.98 (s, 3H), 0.97–0.92 (m, 18H), 0.69–0.58 (m, 12H).
^{13}C NMR : (126 MHz, $CDCl_3$)	220.6, 143.1, 140.5, 120.4, 119.6, 81.2, 79.5, 75.9, 75.3, 64.8, 47.9, 47.2, 41.3, 38.9, 35.9, 33.9, 31.6, 28.9, 18.9, 17.0, 7.1, 7.0, 5.3, 5.1.
FTIR, cm^{-1}: (thin film)	2955 (s), 2876 (s), 1742 (s), 1622 (s), 1456 (m), 1238 (m).
HRMS: (ESI)	Calcd for $(C_{33}H_{57}NO_4Si_2+H)^+$ 588.3899 Found 588.3889.
TLC (1:1 hexanes–ethyl acetate)	R_f = 0.66 (UV, *p*-anisaldehyde)

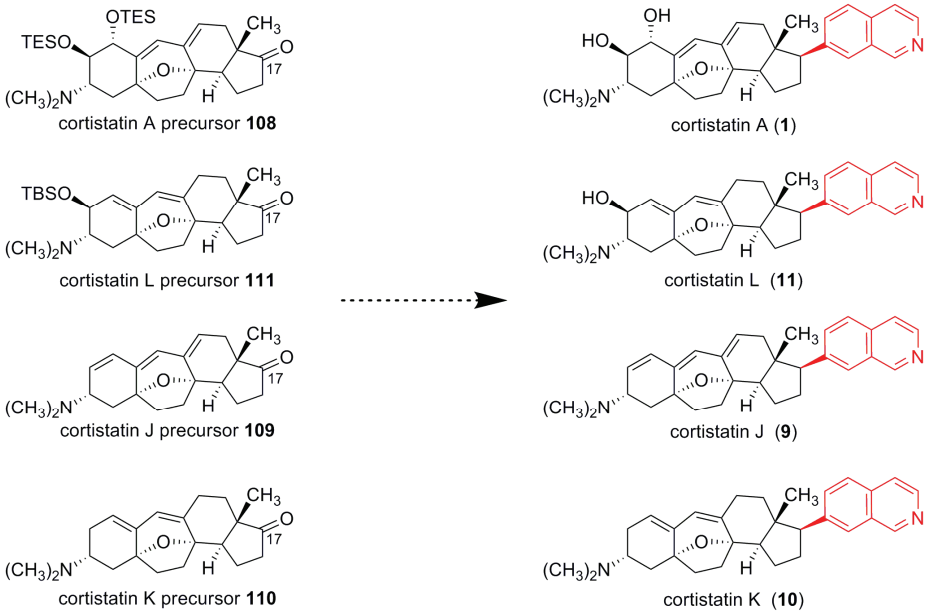
Chapter 3

Synthesis of Cortistatins A, J, K, and L, and Cortistatin Based Affinity Reagents

Introduction

The previous chapter described an efficient synthesis of the key intermediate **112** on gram scale and the conversion of this azido alcohol into cortistatin A, J, K, and L precursors, representing each of the four natural cortistatin ABC-ring substitution patterns. With these 17-keto precursors in hand, the next stage was to find a generally applicable way to introduce the C17 isoquinoline substituent, which is detailed in this chapter (Figure 3.1).

Figure 3.1 Introduction of the 17-Isoquinolinyl Appendage.

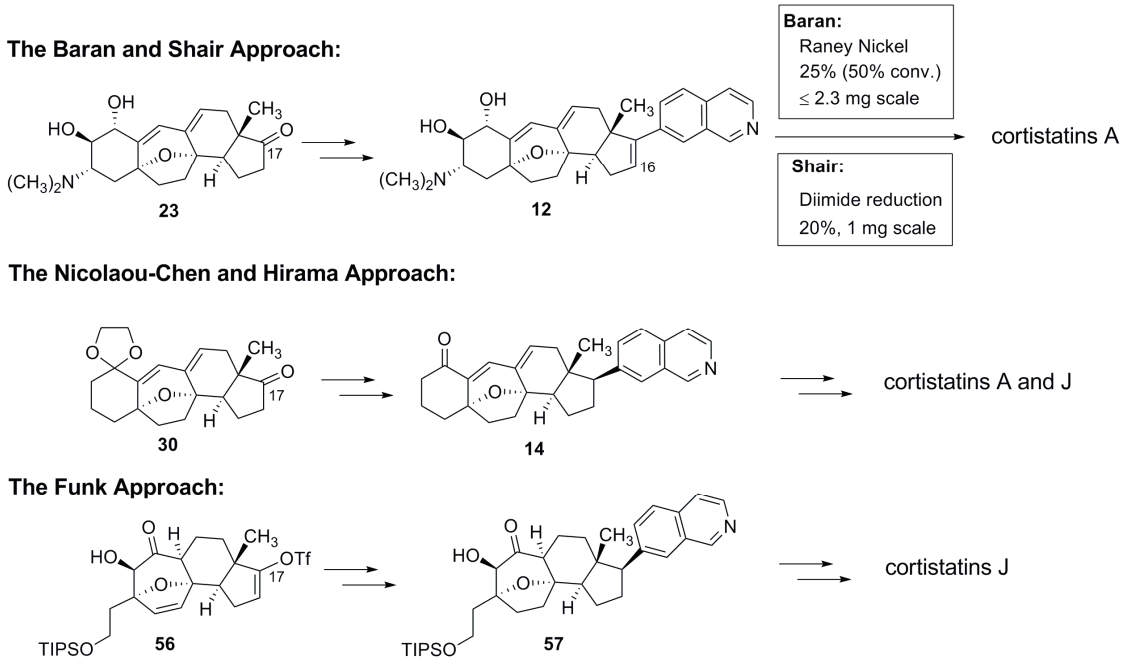


In the published syntheses of cortistatins, different strategies were employed to introduce the isoquinoline moiety (Figure 3.2). The Baran group[1] and the Shair group[2]

[1] (a) Shenvi, R. A.; Guerrero, C. A.; Shi, J.; Li, C.-C.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7241–7243; (b) Shi, J.; Manolikakes, G.; Yeh, C.-H.; Guerrero, C. A.; Shenvi, R. A.; Shigehisa, H.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 8014–8027.
[2] Lee, H. M.; Nieto-Oberhuber, C.; Shair, M. D. *J. Am. Chem. Soc.* **2008**, *130*, 16864–16866.

used similar strategies starting from cortistatinone **23**. This ketone was first converted to a vinyl iodide via hydrazone iodination, and the vinyl iodide product was cross-coupled with 7-(trimethylstannyl)-isoquinoline to afford Δ^{16}-cortistatin A (**12**). However, the final selective hydrogenation of the tri-substituted benzylic olefin in the presence of the diene moiety proved to be challenging. Baran and co-workers used Raney nickel reduction in heated methanol to provide cortistatin A in 25% yield with 50% conversion on a 2.3-mg scale,[1] while Shair and co-workers used diimide reduction and obtained cortistatin A with 20% yield on a 1.0-mg scale.[2] Meanwhile, the Nicolaou−Chen group,[3] the Hirama group,[4] and the Funk group[5] introduced the isoquinoline ring early in their syntheses before functionalizing/forming the A-ring (see Chapter 1 for details).

Figure 3.2 Literature Approaches to Introduce the 17-Isoquinolinyl Appendage.



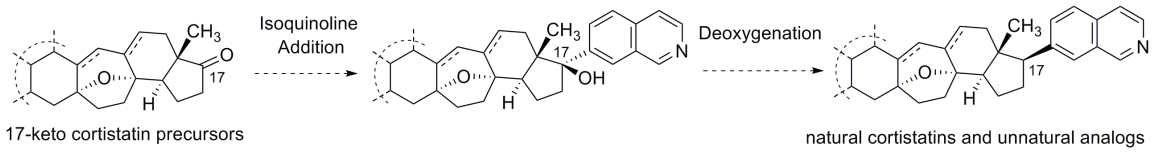
[3] (a) Nicolaou, K. C.; Sun, Y. P.; Peng, X. S.; Polet, D.; Chen, D. Y. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 7310–7313; (b) Nicolaou, K. C.; Peng, X. S.; Sun, Y. P.; Polet, D.; Zou, B.; Lim, C. S.; Chen, D. Y. K. *J. Am. Chem. Soc.* **2009**, *131*, 10587–10597.

[4] Yamashita, S.; Iso, K.; Kitajima, K.; Himuro, M.; Hirama, M. *J. Org. Chem.* **2011**, *76*, 2408–2425.

[5] Nilson, M. G.; Funk, R. L. *J. Am. Chem. Soc.* **2011**, *133*, 12451–12453.

In our synthetic plan, we wished to introduce the 17-isoquinolinyl appendage at the final stage of our synthesis in order to achieve maximum diversification of this important ring appendage with respect to analog preparation. Therefore, we imagined a different strategy by applying an organometallic isoquinoline addition to 17-keto cortistatin precursors (in which the organoletallic reagent would presumably attack from the less hindered bottom face), followed by deoxygenation of the newly formed tertiary C17 alcohol to produce the final products (Figure 3.3).[6] We speculate that in the deoxygenation process, e.g. a radical deoxygenation reaction, the hydrogen radical (or an equivalent) would also come from the less-hindered bottom face to provide the desired stereochemistry at C17. This approach proved to be quite general and was successfully employed in the synthesis of natural cortistatins A, J, K, and L, as well as unnatural cortistatin analogs and affinity probes as detailed in this chapter.

Figure 3.3 Our Approach to Introduce the 17-Isoquinolinyl Appendage.

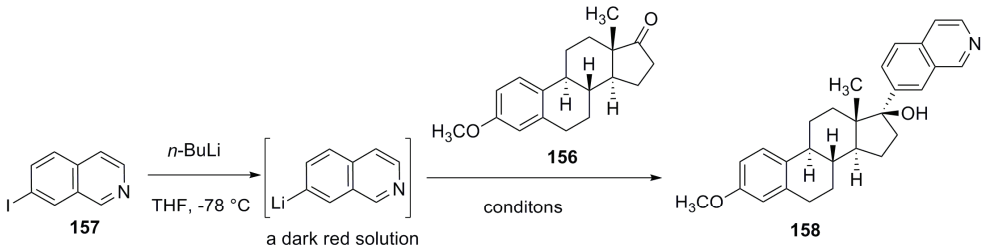


[6] During our work, the Hirama group also used an organometallic isoquinoline addition-deoxygenation sequence to introduce the isoquinoline appendage, although at an earlier stage with an unfunctionalized A-ring (ketone **30**), see: Yamashita, S.; Kitajima, K.; Iso, K.; Hirama, M. *Tetrahedron Lett.* **2009**, *50*, 3277–3279; see also ref 4.

A General Applicable Isoquinoline-Addition-Deoxygenation Sequence to Synthesize Cortistatins A, L, J and K

The readily available 3-*O*-methyl estrone **156** was selected as a model system to study the organometallic isoquinoline addition (Scheme 3.1). 7-Iodoisoquinoline (**157**) was prepared by iodination of 7-trimethylstannylisoquinoline as detailed in the experimental section. It was found that when a solution of 7-iodoisoquinoline (**157**) in tetrahydrofuran at –78 ºC was treated with 1 equiv of *n*-butyllithium, it underwent lithium-halogen exchange to generate a dark red solution within 30 min; without any additives, this 7-lithioisoquinoline reagent did not add to the C17 ketone of **156**, presumably because of the more rapid, competing enolization process. A number of additives were thus screened (entries 2−8). While additives like triethylamine (entries 2) or hexamethylphosphoramide (HMPA, entries 3) did not benefit the reaction, *N*,*N*,*N'*,*N'*-

Scheme 3.1 Isoquinoline Additions to an Estrone Model System.



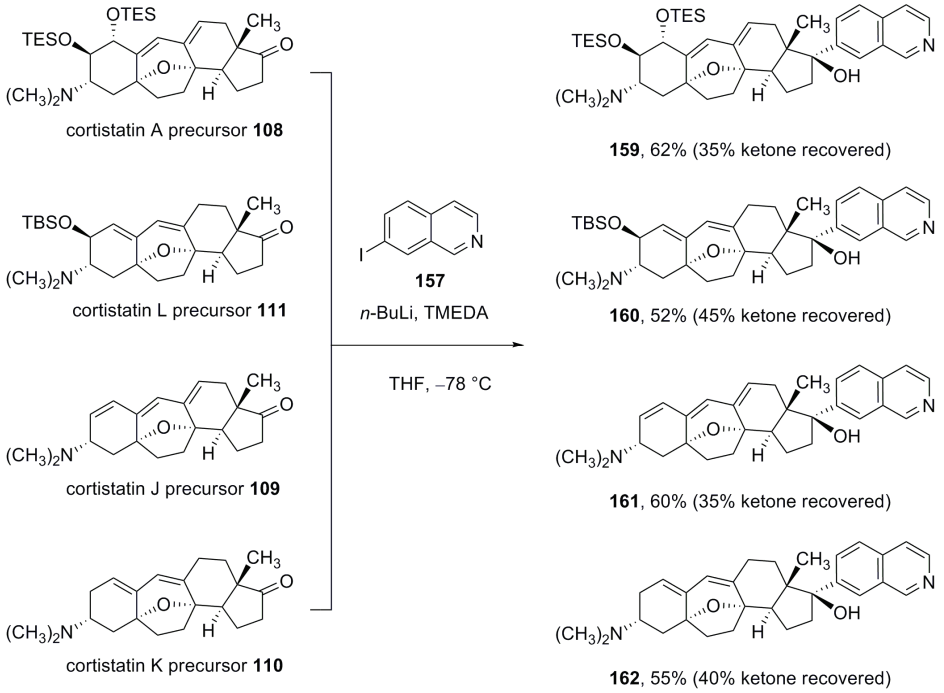
Entry	Conditions	Yield*
1	only **156**, –78 → 23 °C	<10% (80% SM)
2	NEt_3 then **156**, –78 → 23 °C	<10% (80% SM)
3	HMPA then **156**, –78 → 23 °C	<10% (80% SM)
4	TMEDA then **156**, –78 °C	60% (35% SM)
5	a mixture of $BF_3{\cdot}Et_2O$ and **156**, –78 °C	40% (30% SM)
6	a mixture of $La(OTf)_3$ and **156**, –78 °C	35% (25% SM)
7	a mixture of $CeCl_3{\cdot}2LiCl$ and **156**, –78 °C	35% (40% SM)
8	$CeCl_3$ (slurry) then **156**, –78 °C	<10% (80% SM)

* yield was determinded by NMR using an internal standard.

tetramethylethylenediamine (TMEDA), a reagent used by Jaouen and co-workers to complex with differently substituted phenyllithium reagents to improve their addition to a similar 17-keto steroid system,[7,8] was found to effectively promote the nucleophilic addition, in which 60% of the addition product **158** was obtained (as a single diastereomer) along with 35% of the starting ketone recovered (entry 4).

This isoquinoline addition protocol was successfully applied to the natural cortistatin system (Scheme 3.2). After complexation to TMEDA (15 equiv), 7-lithio-isoquinoline (5 equiv) added to 17-keto cortistatin precursors to provide the corresponding addition products **159**, **160**, **161**, and **162** in 52–62% yield, along with 35–

Scheme 3.2. Isoquinoline Additions to Cortistatin A, L, J, and K Precursors.



[7] Foy, N.; Stephan, E.; Vessieres, A.; Salomon, E.; Heldt, J. M.; Huche, M. ; Jaouen, G. *Chembiochem,* **2003**, *4*, 494–503.

[8] During our work, the Baran group also reported a similar reaction condition by lithiation of 7-bromoisoquinoline and then complexation to TMEDA to enable its addition to 17-ketone in a cortistatin system, see: Shi, J.; Shigehisa, H.; Guerrero, C. A.; Shenvi, R. A.; Li, C. C.; Baran, P. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 4328–4331.

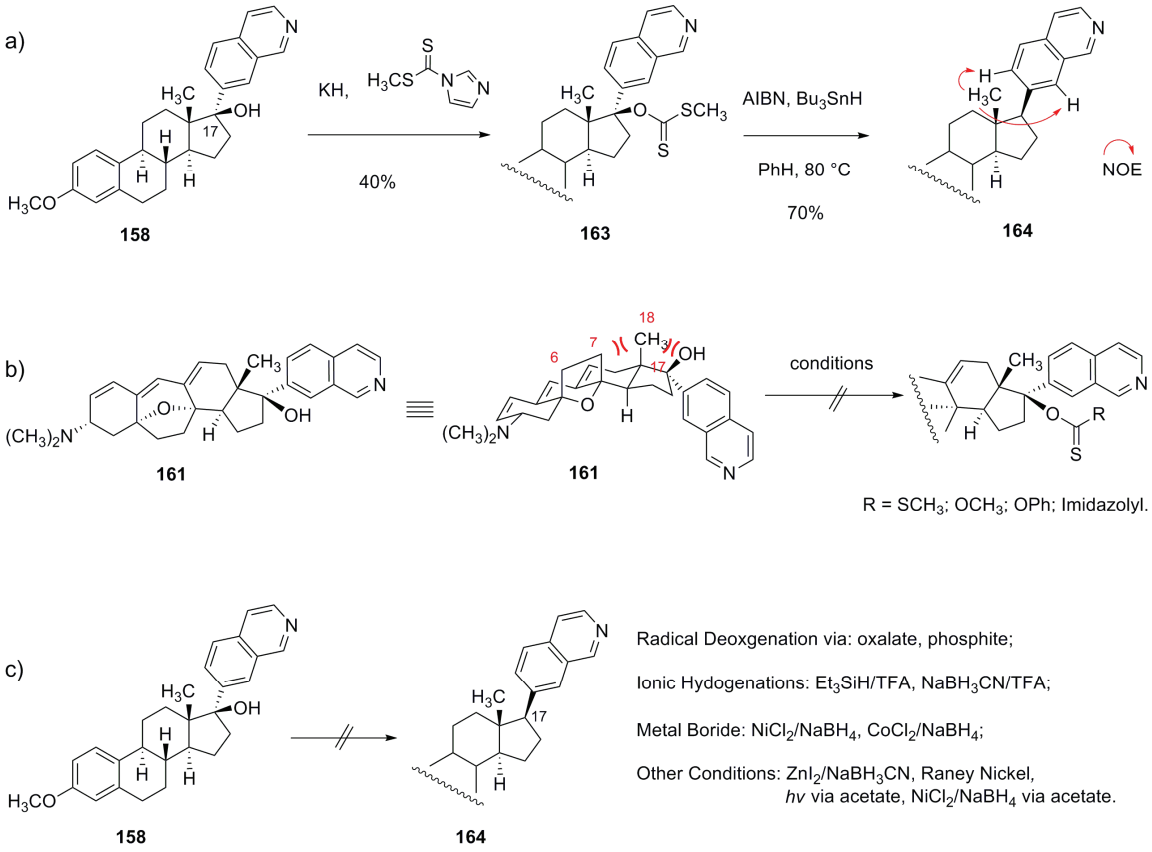
45% of the starting ketone recovered. The recovered ketones could be re-subjected to the isoquinoline addition condition, and after a typical 3-cycle procedure, >80% overall yield of the addition products could be obtained for the addition.

Now that the isoquinoline addition was working, the next step would be removing the C17 hydroxyl group. Barton deoxygenation conditions were first tried (Scheme 3.3a).[9] In the model system, xanthate **163** was formed with excess potassium hydride and 1-(methyldithiocarbonyl)imidazole in a modest yield (about 20% of elimination product was also obtained), and subsequent radical deoxygenation went on smoothly, affording the desired deoxygenated 17-(*S*) product **164** as a single diastereomer, in which the hydrogen radical presumably came from the less hindered bottom face as expected (the stereochemistry was proved by NOE studies). However, in every attempt to apply this and a number of other conditions to make the xanthate or other thiocarbonyl derivatives of the real cortistatin J system, no desired product could be formed. This was thought to be due to the more sensitive starting material as well as a more hindered C17 tertiary alcohol (likely because of the push from the C6,C7 carbon bridge to the C18 angular methyl group and then to the C17 alcohol, Scheme 3.3b). Many other conditions were screened (Scheme 3.3c). Several ionic hydrogenation[10] and metal boride reduction conditions[11] resulted in the reduction of the isoquinoline ring first. A reported general zinc iodide-sodium cyanoborohydride mediated reduction of benzylic alcohols afforded

[9] For a general review of Barton radical deoxygenation, see: Hartwig, W. *Tetrahedron* **1983**, *39*, 2609–2645.
[10] (a) Kursanov, D. N.; Parnes, Z. N.; Loim, N. M. *Synthesis* **1974**, 633–651;(b) Layton, M. E.; Morales, C. A.; Shair, M. D. *J. Am. Chem. Soc.* **2002**, *124*, 773–775.
[11] He, Y.; Pan, X.; Wang, S.; Zhao, H. *Synth. Commun.* **1989**, *19*, 3051–3054.

only returning starting material.[12] Raney Nickel[13,14] and photochemistry via acetates[15] were also unsuccessful in our hands.

Scheme 3.3 Attempts to Remove C17 Hydroxyl Group with Barton Radical Deoxygenation and Other Conditions.

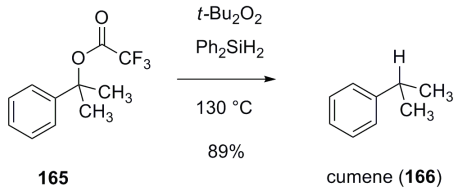


Given the initial modest success in the model system, we decided to turn our attention back to the radical deoxygenation process, which is ideal with its mild reaction condition, orthogonality to all the functional groups, and a presumably stable radical

[12] Lau C. K.; Dufresne, C.; Belanger, P. C.; Pietre, S.; Scheigetz, J. *J. Org. Chem.* **1986**, *51*, 3038–3043.
[13] Krafft, M. E.; Crooks, W. J., III; Zorc, B.; Milczanowski, S. E. *J. Org. Chem.* **1988**, *53*, 3158–3163.
[14] During our work, the Baran group reported a Raney Nickel mediated deoxygenation of the benzylic, tertiary alcohol, but giving the wrong stereochemistry at C17 position, see Ref 8.
[15] Deshayes, H.; Pete, J.; Portella C.; Scholler. D. *J. Chem. Soc. Chem. Commun* **1975**, 439–440.

intermediate at the tertiary, benzylic C17 position. What we needed was to find an easily obtained activating group to activate the hindered C17 tertiary alcohol. Initial attempts with C17 alcohol derived oxalate [16] or phosphate [17] led to complex decomposition (Scheme 3.3c). After extensive literature search, we found that Jiang and co-workers reported a radical deoxygenation condition with readily available trifluoroacetates (Scheme 3.4).[18] For instance, when trifluoroacetate **165** was heated with di-*tert*-butyl peroxide (1 equiv, as the radical initiator) in diphenylsilane as a solvent (as the hydrogen donor) at 130 ºC, a smooth radical deoxygenation occurred within 12 h to provide cumene (**166**) in excellent yield.

Scheme 3.4 Jiang's Radical Deoxygenation with Trifluoroacetates.



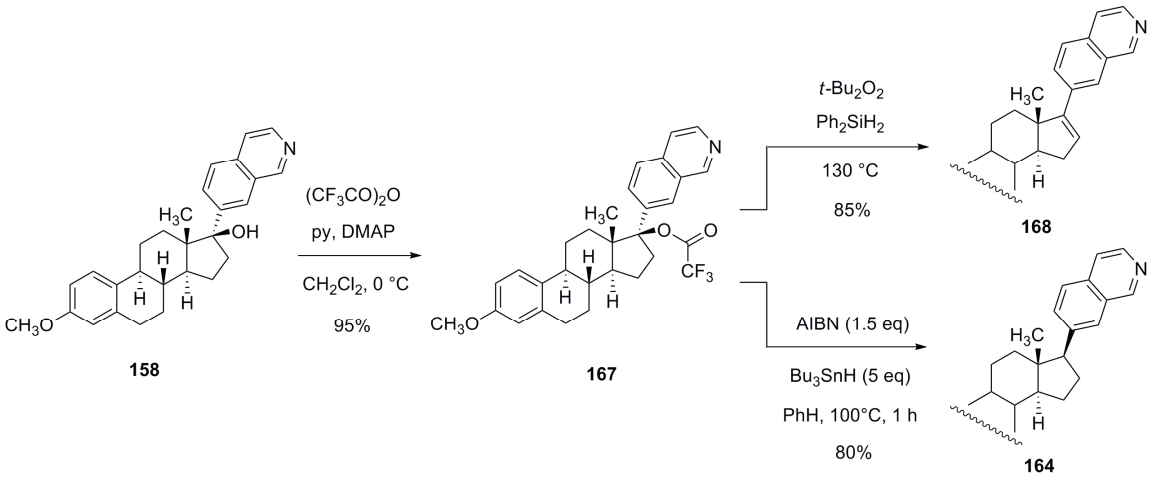
165 cumene (**166**)

This promising protocol was first applied to the estrone model system (Scheme 3.5). The trifluoroacetate **167** was readily prepared by stirring tertiary alcohol **158** with trifluoroacetic anhydride (5 equiv) in the presence of pyridine (10 equiv) and 4-dimethylaminopyridine (DMAP, 0.5 equiv) in dichloromethane at 0 ºC for 0.5 h in almost quantitative yield. However, when this trifluoroacetate **167** was subjected to the Jiang's condition with di-*tert*-butyl peroxide (1−3 equiv) in diphenylsilane as a solvent at 130 ºC,

[16] Lecomte, V.; Stephan, E.; Rager, M.-N.; Jaouen, G. *J. Org.Chem.* **2004**, *69*, 3216–3219.
[17] Zhang, L.; Koreeda, M. *J. Am. Chem. Soc.* **2004**, *126*, 13190–13191.
[18] (a) Jang, D. O.; Kim, J. G.; Cho, D. H.; Chung, C. M *Tetrahedron Lett.* **2001**, *42*, 1073–1075; (b) Kim, J. G.; Cho, D. H.; Jang, D. O. *Tetrahedron Lett.* **2004**, *45*, 3031–3033.

only the elimination product **168** was obtained. It was speculated that the high temperature employed in this reaction might caused the exclusive elimination in our system. Therefore, azobisisobutyronitrile (AIBN, 1.5 equiv), a radical initiator that could be triggered at much lower temperature,[19] was employed with a commonly used hydrogen donor, tributyltin hydride (5 equiv) in heated benzene at 100 ºC in a sealed tube. To our delight, a clean radical deoxygenation proceeded and the starting trifluoroacetate was consumed within 1 h, affording the desired product **164** with 17-(*S*) configuration as a single diastereomer in 80% yield, along with less than 10% elimination product **168**. It was found that the use of excess radical initiator and hydrogen donor was necessary for the reaction, otherwise leading to much more elimination product. The reaction temperature was also critical, as reaction at 120 ºC (1 h) resulted in more elimination

Scheme 3.5 Deoxygenation with Trifluoroacetate **167** in an Estrone Model System.

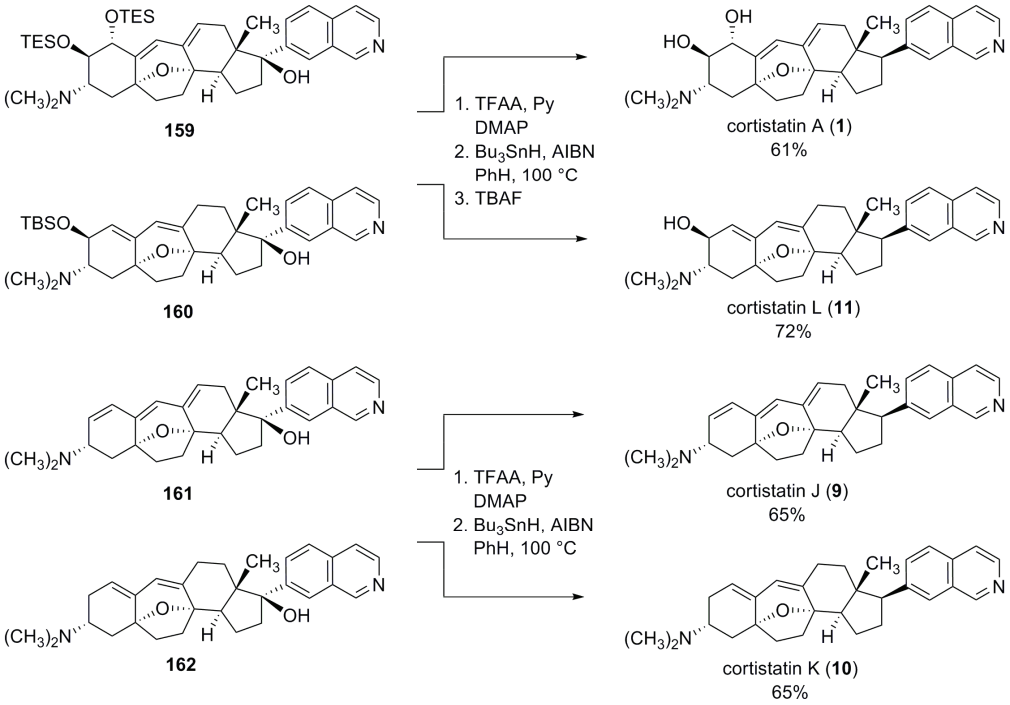


[19] The half life ($t_{1/2}$) of di-*tert*-butyl peroxide at 130 ºC is 6.4 h, at 100 ºC is 219 h; while the $t_{1/2}$ of AIBN is 0.13 h at 100 ºC, 1.0 h at 80 ºC; for a complete chart, see: Polymer Handbook, Eds. Brandrup, J; Immergut, E.H.; Grulke, E.A., 4th Edition, John Wiley, New York, 1999, II/2-69 or the Sigma-Aldrich online chart: "Applications: Free Radical Initiators".

product (>40%) while reaction at 80 ºC (12 h) led to mostly the recovered starting trifluroacetate.

The optimized reaction condition was successfully translated to the real cortistatin system (Scheme 3.6). The C17 tertiary alcohol of addition products **159**, **160**, **161**, and **162** were readily transformed to the corresponding trifluoroacetates using the previous condition with excess trifluoroacetic anhydride (5 equiv) in the presence of pyridine (10 equiv) and 4-dimethylaminopyridine (DMAP, 0.5 equiv) in dichloromethane at 0 ºC; following radical deoxygenation with azobisisobutyronitrile (AIBN, 1.5 equiv) and excess tributyltin hydride (5−10 equiv) in benzene at 100 ºC for 1−2 h led to the desired deoxygenated products with the correct 17-(*S*) configuration in 60–70% yield over two steps (about 10% of the corresponding elimination products were also observed). In the cortistatin J and K series, deoxygenation led to these substances directly; while in the

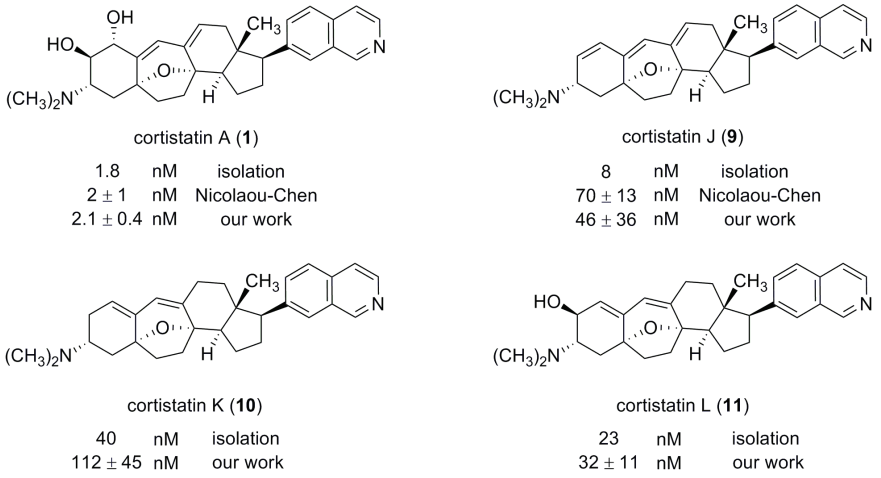
Scheme 3.6 Syntheses of Cortistatin A, L, J, and K.



cortistatin A and cortistatin L series, a final cleavage of the silyl ether protective group(s) with tetra-*n*-butylammonium fluoride (TBAF) at 23 ºC afforded the desired natural products in good yields. In all cases, spectroscopic data for the synthetic materials matched values reported for the natural products; and by employing this sequence, we were able to prepare 20 mg of cortistatin A in a single batch.

In addition to spectroscopic characterization, synthetic cortistatins A, J, K, and L were evaluated for their ability to inhibit the growth of HUVECs in culture (Figure 3.4). My co-worker, Dr. Ge Zou measured the GI_{50} values after a 96-h incubation. It was found that for synthetic cortistatin A, we observed growth inhibition of HUVECs consistent with reported values,[20] while measurements for synthetic cortistatin J more closely matched reports from the Nicolaou–Chen group[3b] than initial reports,[21] and GI_{50} values for synthetic cortistatins K and L fell within the range of those originally reported to slightly higher.[21]

Figure 3.4 GI_{50} Values of Natural and Synthetic Cortistans against HUVECs.

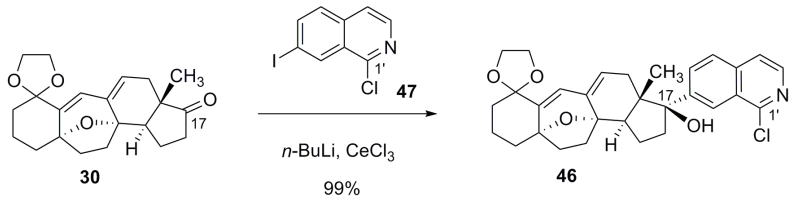


[20] Aoki, S.; Watanabe, Y.; Sanagawa, M.; Setiawan, A.; Kotoku, N.; Kobayashi, M. *J. Am. Chem. Soc.* **2006**, *128*, 3148–3149.
[21] Aoki, S.; Watanabe, Y.; Tanabe, D.; Setiawan, A.; Arai, M.; Kobayashi, M. *Tetrahedron Lett.* **2007**, *48*, 4485–4488.

An Improved Synthesis of Cortistatin A

During our work, the Hirama group reported an efficient cerium (III) chloride promoted isoquinoline addition to C17 ketone in a cortistatin system (Scheme 3.7).[6] 1-Chloro-7-iodo isoquinoline (**47**) and *n*-butyllithium was added sequentially to a slurry of anhydrous cerium (III) chloride in tetrahydrofuran at –78 ºC to afford an isoquinoline derived organocerium reagent,[22] which add to ketone **30** in almost quantitative yield. The authors found that incorporation of 1'-chloride in the isoquinoline was important to prevent the C1' addition in the reaction conditions; when 7-iodo-isoquinoline (**157**) was subjected to the same reaction condition, no addition product could be observed, which was in consistent with our own observations (Scheme 3.1, entry 8).

Scheme 3.7 Hirama's Isoquinoline Addition Condition with Cerium (III) Chloride.

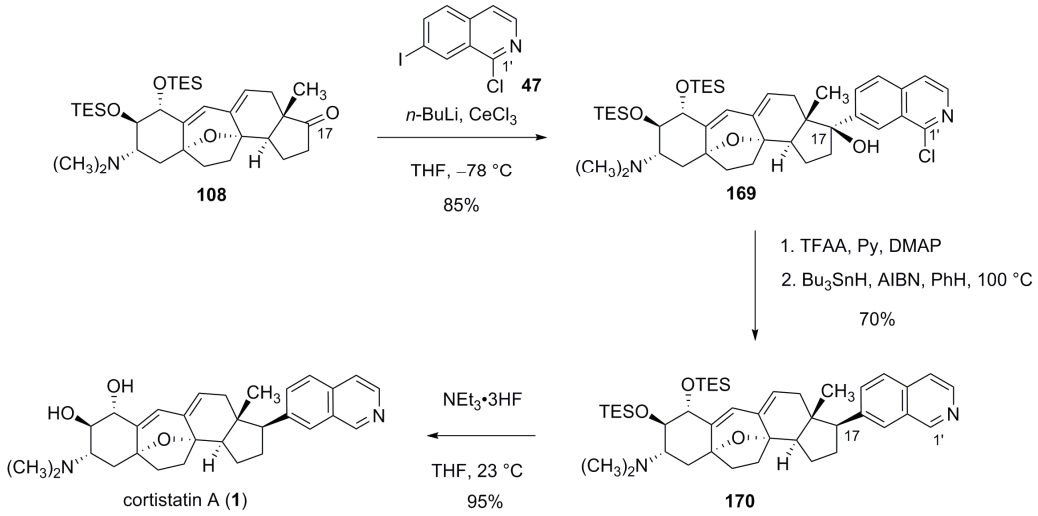


We thought applying Hirama's condition in our fully functionalized cortistatin system would effect a more efficient isoquinoline addition; we also envisioned that we should be able to remove the C1' chloride in our radical deoxygenation step (Scheme 3.8). To our delight, Hirama's organocerium reagent derived from 1-chloro-7-iodo isoquinoline (**46**) also effectively added to the C17 ketone in the cortistatin A precursor

[22] Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392–4398.

108 to afford the addition product **169** in 85% yield. After trifluoroacetate formation, the subsequent radical deoxygenation with azobisisobutyronitrile (AIBN, 3 equiv) and excess tributyltin hydride (15 equiv) in benzene at 100 ºC also cleaved the C1' chloride as expected, providing protected cortistatin A **170** in 70% yield over two steps. The final deprotection with triethylamine trihydrofluoride[23] furnished cortistatin A (**1**) in 95% yield on a 10.8-mg batch.

Scheme 3.8 An Improved Synthesis of Cortistatin A.



Synthesis of Cortistatin Probes and Their Use in Target Identification

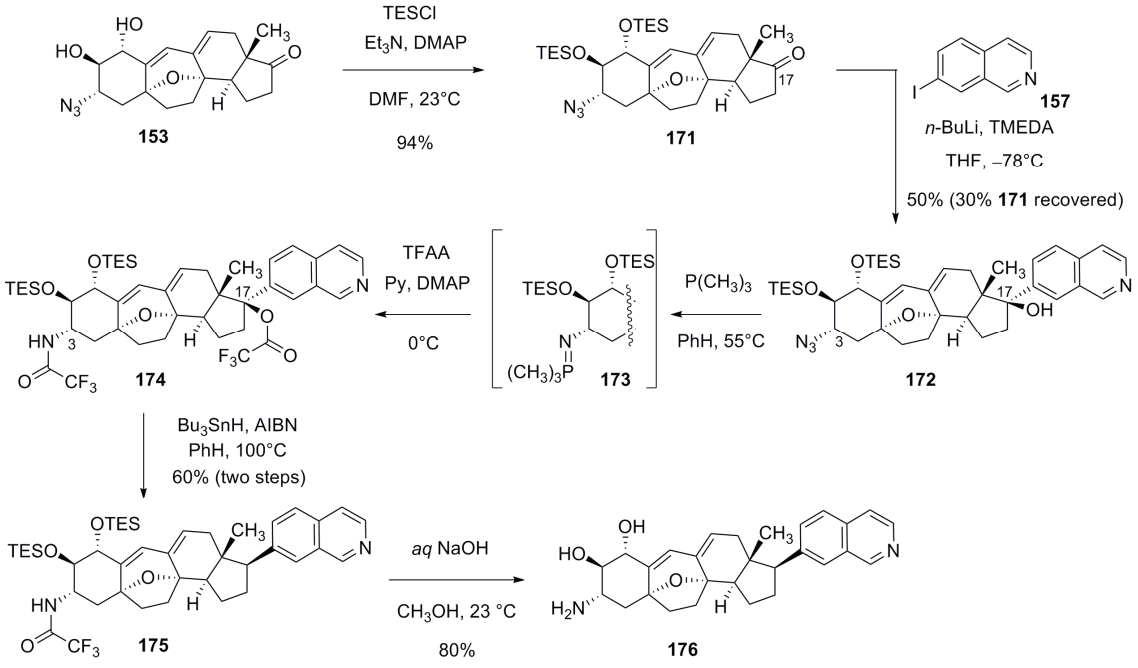
To date, the mechanism of action of the cortistatins on inhibition of HEVECs remained unclear. An objective of our research was the synthesis of cortistatin-based biological probes and their use to identify the biological target(s) of this class of natural

[23] In the previous tetra-*n*-butylammonium fluoride (TBAF)-mediated deprotection procedure, TBAF was found to co-spot with the final natural product, which makes the purification step difficult.

products. After study the preliminary SAR data of cortistatins (see Chapter 1 for details), we identified C3 amino group as a suitable place to install an affinity isolation tag which is likely to be far away from the binding site as suggested by Nicolaou-Chen's homology model.[24] Therefore, synthesis of a cortistatin A based C3-primary amine **176** was carried out (Scheme 3.9).

Our synthesis commenced from the azido transdiol **153** (prepared in 6 steps from key intermediate **112** as described in Chapter 2). The diol was bis-protected with chlorotriethylsilane to provide intermediate **171**; TMEDA-mediated 7-lithioisoquinoline addition to the C17 ketone of **171** proceeded smoothly, affording tertiary alcohol **172** in 50% yield, along with 30% of ketone **171** recovered. The subsequent reduction of the hindered C3 azide was not straightforward. After much experimentation, an optimized

Scheme 3.9 Synthesis of a Cortistatin A Primary Amine **176**.

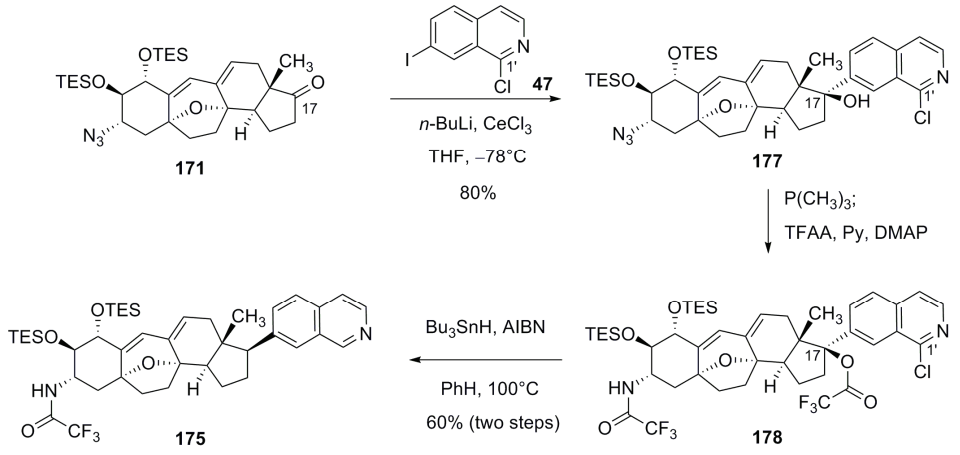


[24] Cee, V. J.; Chen, D. Y. K.; Lee, M. R.; Nicolaou, K. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 8952–8957.

procedure was developed, in which azide **172** was first heated with excess anhydrous trimethylphosphine (5 equiv) in benzene at 55 ºC for 2 h to effect its complete conversion to an iminophosphine intermediate **173**;[25] without isolation, the reaction mixture was cooled in an ice-bath and sequentially treated with pyridine (20 equiv), DMAP (1 equiv), followed by trifluoroacetic anhydride (TFAA, 10 equiv), to furnish a trifluoroacetamide **174** with the C17 alcohol also trifluoroacetylated in the same operation. Subsequent radical deoxygenation with azobisisobutyronitrile (AIBN, 1.5 equiv) and excess tributyltin hydride (8 equiv) in benzene at 100 ºC cleaved the C17 trifluoroacetate as expected, providing intermediate **175** in 60% yield over two steps. Finally, a global deprotection by stirring **175** in a 4:1 mixture of methanol and 1N aqueous sodium hydroxide afforded a cortistatin A C3 primary amine **176** in 80% yield.

The isoquinoline addition to ketone **171** could be further improved by employing Hirama's organocerium reagent (Scheme 3.10). Despite a potentially reactive azide group at C3, the organocerium reagent derived from 1-chloro-7-iodo isoquinoline (**47**) added to

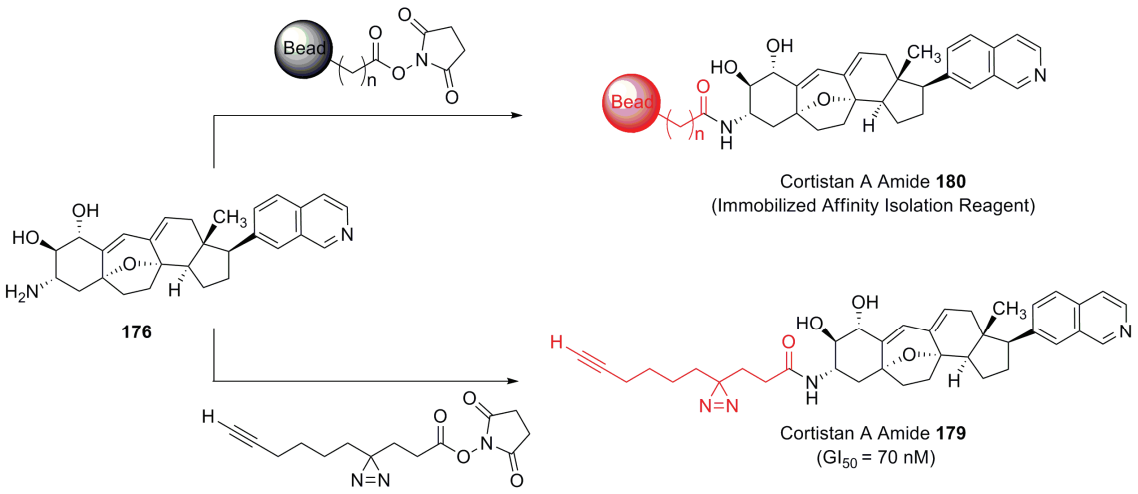
Scheme 3.10 Synthesis of Intermediate **175** Using Hirama's Organocerium Reagent.



[25] Addition of water with trimethlyphosphine led to complex decomposition of the starting material.

the C17 ketone exclusively at −78 ºC to give tertiary alcohol product **177** in 80% yield. The same Staudinger-trifluoroacetylation sequence afforded **178**, and subsequent radical deoxygenation-dehalogenation with azobisisobutyronitrile (AIBN, 3 equiv) and excess tributyltin hydride (20 equiv) at 100 ºC proceeded uneventfully, providing the same intermediate **175** in 60% yield over two steps.

Scheme 3.11 Preparation of Cortistatin A Based Affinity Reagents.

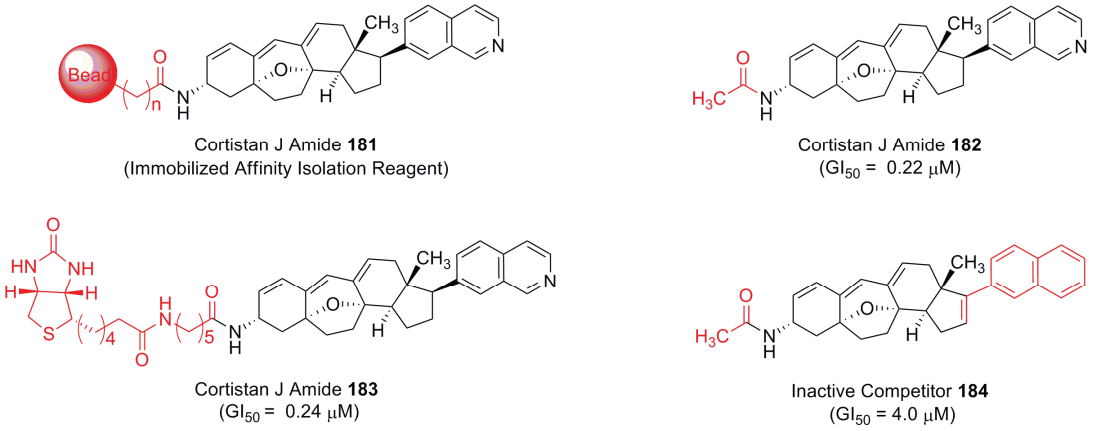


The cortistatin A amine **176** was subsequently linked to sepharose beads with an activated *N*-hydroxysuccinimide (NHS) ester to provide an immobilized affinity isolation reagent **179**; this amine was also converted to amide **180** containing a diazirine as a photo-cross-linker[26] and a terminal alkyne as a cycloaddition partner,[27] which could potentially be used for target identification studies in live cells (by Dr. Ge Zou, Scheme 3.11).[28] In addition, a cortistatin J derived C3 primary amine **186** (prepared using the

[26] (a) Dilly, S. J.; Bell, M. J.; Clark, A. J.; Marsh, A.; Napier, R. M.; Sergeant, M. J.;A. J. Thompson and P. C. Taylor, *Chem. Commun.* **2007**, 2808–2810; (b) Smith, D. P.; Anderson, J.; Plante, J.; Ashcroft, A. E.; Radford, S. E.; Wilson A. J.; Parker, M. J. *Chem. Commun.* **2008**, 5728–5730.
[27] Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021.
[28] Shi, H.; Zhang, C.-J.; Chen, G. Y. J.; Yao, S. Q. *J. Am. Chem. Soc.* **2012**, *134*, 3001–3014.

same isoquinoline-addition-radical-deoxygenation sequence by Dr. Ge Zou) was also transformed to an immobilized affinity isolation reagent **181**, and amides **182** and **183**; an Δ^{16}, naphthalene-containing inactive competitor **184** was also synthesized (Figure 3.5). Interestingly, amides **180**, **182** and **183** were all about 5−20 fold less active than the parent natural products even with a large substitution group at C3, indicating that the immobilized reagents **179** and **181** were also likely to be active; while naphthalene-containing amide **184** was another 18 fold less active than the isoquinoline-containing amide **182**.[29]

Figure 3.5 Cortistatin J Based Affinity Isolation Reagents and Related Amides.

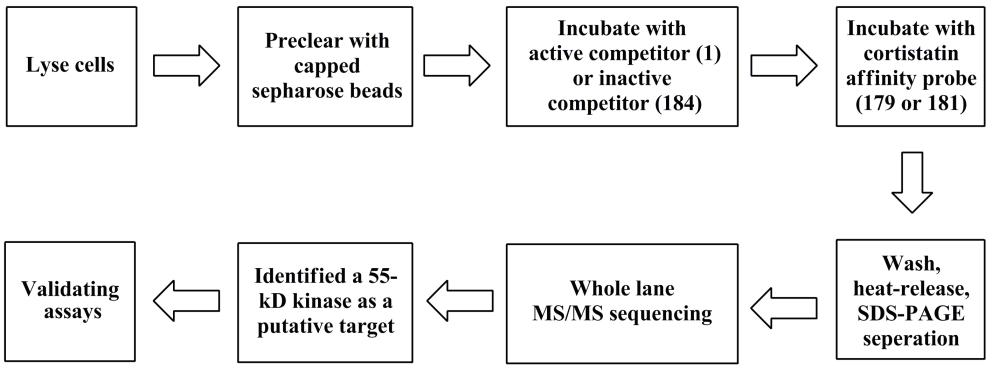


The immobile affinity reagents **179** and **181** were subsequently used by Dr. Ge Zou in pull-down experiments in HUVEC and HEK293T cell lysates to identify the molecular target(s) of cortistatins as depicted in Figure 3.6. In theory, the cortistatin target protein(s) should be pulled down by an affinity reagent alone, or by the affinity

[29] The C16,C17 double bond were not likely to be responsible for loss of much activity, as suggested by the good GI_{50} of Δ^{16}-cortistatin A (**12**) identified by Baran and co-workers: Shi, J.; Shigehisa, H.; Guerrero, C. A.; Shenvi, R. A.; Li, C. C.; Baran, P. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 4328–4331.

reagent in the presence of the negative competitor **184**; but should not be pulled down when the active competitor cortistatin A (**1**) was added. By applying these principles, a 55-kD, membrane kinase was identified as a putative cortistatin target after initial validation studies. Further validations of this protein target and *in vivo* pull-down experiments using affinity reagent **180** are currently underway.

Figure 3.6 Pull-down Experiments with Cortistatin Based Affinity Isolation Reagents.



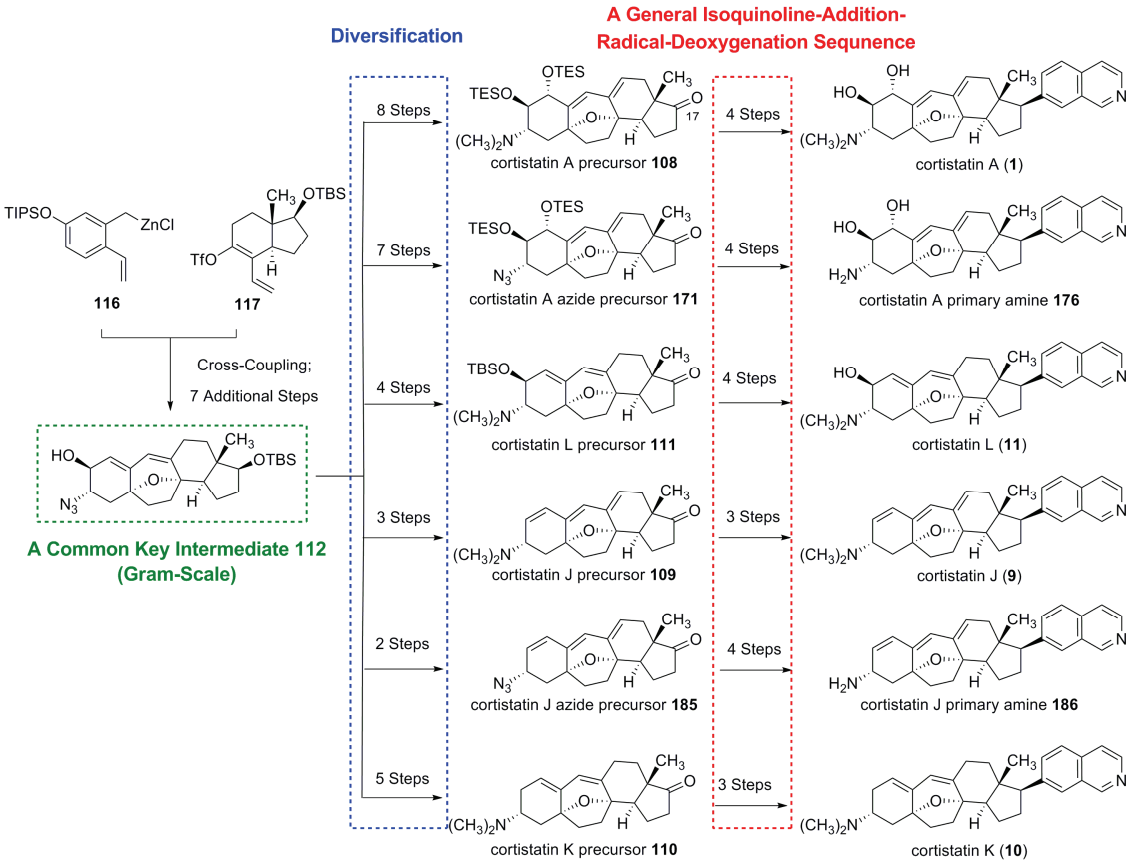
Description	Peptide Counts from HEK293T Pull Down		
	only probe (**179** or **181**)	probe + cortistatin A (**1**)	probe + inactive competitor (**184**)
55-kD protein	12	0	11

Conclusion

Our synthesis of cortistatin alkaloids are summarized in Figure 3.7. We developed a robust synthetic route to prepare gram quantities of key intermediate **112** starting from readily available benzylzinc reagent **116** and enol triflate **117**. This key intermediate **112** was then successfully diversified to different cortistatin 17-keto precursors **108**, **109**, **110**, and **111**, representing each of the four natural occurring cortistatin ABC-ring substitution

patterns; **112** was also converted to ketones **171** and **185**, which retained the C3 azido group as a handle for further functionalization. Subsequently, a general applicable, isoquinoline-addition-radical-deoxygenation sequence was developed to introduce the C17 isoquinoline substituent at the final stage of our synthesis. By applying this strategy, natural products cortistatin A (**1**), J (**9**), K (**10**), and L (**11**) were prepared, as well as a number of unnatural cortistatin analogs and cortistatin primary amines **176** and **186**. These primary amines were used to prepare several biological probes. By employing these probes in pull-down experiments, we identified a 55-kD membrane kinase as a putative protein target of cortistatins.

Figure 3.7 Summary of the Syntheses of Cortistatin Alkaloids.



Experimental Section

General Experimental Procedures. All reactions were performed in round-bottomed flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation (house vacuum, ca. 25–40 Torr) at ambient temperature, unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60 Å pore-size, 230–400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light, then were stained with either an aqueous sulfuric acid solution of ceric ammonium molybdate (CAM) or acidic ethanolic *p*-anisaldehyde solution (*p*-anisaldehyde) then briefly heated on a hot plate. Flash-column chromatography was performed as described by Still et al.,[30] employing silica gel (60 Å, 32–63 μM, standard grade, Dynamic Adsorbents, Inc.).

Materials. Commercial solvents and reagents were used as received with the following exceptions. Tetramethylethylenediamine (TMEDA) weas distilled from calcium hydride under an atmosphere of argon. Tetrahydrofuran, dichloromethane, benzene, toluene, dioxane, and ether were purified by the method of Pangborn et al.[31] *N*-Bromosuccinimide was recrystallized from water. The molarity of *n*-butyllithium solutions was determined by titration against a standard solution of diphenylacetic acid in tetrahydrofuran (average of three determinations).[32]

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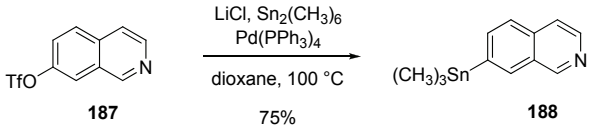
[30] Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
[31] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.
[32] Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879–1880.

Instrumentation. Proton magnetic resonance (^{1}H NMR) spectra were recorded on Varian INOVA 500 (500 MHz) or 600 (600 MHz) NMR spectrometers at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26; C_6D_5H, δ 7.15). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br = broad, app = apparent), integration, and coupling constant (*J*) in Hertz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on Varian INOVA 500 (126 MHz) NMR spectrometers at 23 °C. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, δ 77.0; C_6D_6, δ 128.0). Infrared (IR) spectra were obtained using a Shimadzu 8400S FT-IR spectrometer and were referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (vs = very strong, s = strong, m = medium, w = weak, br = broad). High-resolution mass spectra were obtained at the Harvard University Mass Spectrometry Facility. High performance liquid chromatography purifications were performed using an Agilent Technologies 1200 Series preparative HPLC system. Optical rotations were measured using a 2-mL cell with a 10-cm path length on a Jasco DIP 370 digital polarimeter.

*(For clarity, intermediates that have not been assigned numbers in the text are numbered sequentially in the experimental section beginning with **187**).*



187 188

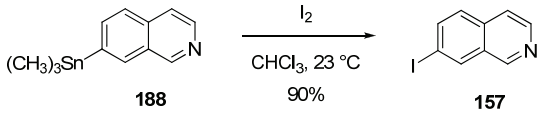
7-Trimethylstannylisoquinoline (**188)**.

Hexamethylditin (1.20 mL, 5.73 mmol, 1.1 equiv) was added to a solution of 7-isoquinolyl trifluoromethylsulfonate (**187**)[33] (1.44 g, 5.21 mmol, 1 equiv), lithium chloride (1.33 g, 31.3 mmol, 6 equiv), and tetrakis(triphenylphosphine)palladium(0) (600 mg, 0.521 mmol, 0.1 equiv) in dioxane (10.4 mL). The reaction mixture was degassed by sparging for 20 min with a slow stream of argon gas through a 22-gauge stainless steel. The flask was capped with a glass stopper under argon and the stopped flask was sealed with Teflon® tape and then Parafilm®. After sealing, the reaction flask was placed in an oil bath preheated to 100 ºC. After 5 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. Solids were removed by filtration through a pad of Celite, washing with ethyl acetate (3 × 30 mL). The filtrates were combined and the combined organic solution was concentrated. The residue was purified by flash-column chromatography (7:1 hexanes–ethyl acetate initially, grading to 5:1 hexanes–ethyl acetate, then 3:1 hexanes–ethyl acetate) to furnish 7-trimethylstannylisoquinoline (**188)** as a pale yellow solid (1.14 g, 75%).

^{1}H NMR:	9.23 (s, 1H), 8.50 (dd, 1H, *J* = 6.0, 0.9 Hz), 8.09 (m,
(500 MHz, $CDCl_3$)	1H), 7.81–7.74 (m, 2H), 7.60 (d, 1H, *J* = 6.0 Hz), 0.38

[33] 7-isoquinolyl trifluoromethylsulfonate (**187**) was prepared as reported: Denni-Dischert, D.; Marterer, W.; Baenziger, M.; Yusuff, N.; Batt, D.; Ramsey, T.; Geng, P.; Michael, W.; Wang, R. B.; Taplin, F., Jr.; Versace, R.; Cesarz, D.; Perez, L. B. *Org. Process Res. Dev.* **2006**, *10*, 70–77.

	(m, 9H).
^{13}C NMR : (126 MHz, $CDCl_3$)	152.3, 142.9, 142.2, 136.8, 135.5, 128.3, 125.4, 120.3, –9.5.
FTIR, cm^{-1}: (thin film)	3047 (m), 2982 (s), 2913 (m), 1618 (s), 1402 (m), 1337 (m).
HRMS: (ESI)	Calcd for $(C_{12}H_{15}NSn+H)^+$ 294.0299 Found 294.0313.
TLC (1:1 hexanes–ethyl acetate)	R_f = 0.57 (UV)



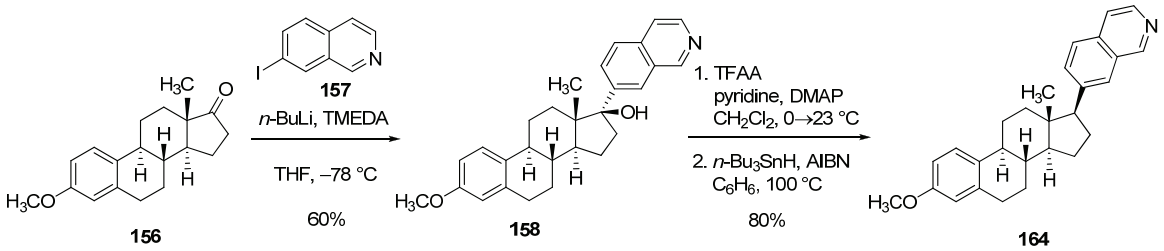
188 157

7-Iodoisoquinoline (**157**).

Iodine (525 mg, 2.07 mmol, 1.1 equiv) was added to a solution of 7-trimethylstannylisoquinoline (**188**) (550 mg, 1.88 mmol, 1 equiv**)** in chloroform (19 mL). After 1 h, a second portion of iodine (52.5 mg, 0.207 mmol, 0.11 equiv) was added. After 1 h, the reaction mixture was partitioned between saturated aqueous sodium thiosulfate solution (20 mL) and ethyl acetate (60 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (30 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (5:1 hexanes–ethyl acetate initially, grading to 3:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate) to afford 7-iodoisoquinoline (**157**) as a white solid (475 mg, 90%).

^{1}H NMR: (500 MHz, $CDCl_3$)	9.14 (s, 1H), 8.54 (d, 1H, J = 6.0 Hz), 8.33 (d, 1H, J = 0.9 Hz), 7.90 (dd, 1H, J = 8.7, 1.8 Hz), 7.58 (d, 1H, J = 6.0 Hz), 7.53 (d, 1H, J = 8.7 Hz).
^{13}C NMR : (126 MHz, $CDCl_3$)	151.2, 143.5, 138.8, 136.4, 134.3, 129.8, 128.0, 120.1, 92.3.

FTIR, cm^{-1}: (thin film)	3057 (m), 2916 (m), 2849 (m), 1562 (s), 1489 (s), 1204 (s).	
HRMS: (ESI)	Calcd for $(C_9H_6IN+H)^+$	255.9618
	Found	255.9620
TLC (1:1 hexanes–ethyl acetate)	R_f = 0.42 (UV)	



Isoquinolyl Estrone (**164**).

A solution of *n*-butyllithium in hexanes (2.50 M, 81 μL, 0.202 mmol, 5 equiv) was added dropwise to a solution of 7-iodoisoquinoline (**157**) (51.6 mg, 0.202 mmol, 5 equiv) in tetrahydrofuran (1.0 mL) at –78 ºC, producing a dark red solution. After 30 min, *N,N,N',N'*-tetramethylethylenediamine (92 μL, 0.607 mmol, 15 equiv) was added. After 10 min, a solution of ketone **156** (11.5 mg, 0.0404 mmol, 1 equiv) in tetrahydrofuran (0.20 mL) was added via cannula. After 30 min, saturated aqueous sodium bicarbonate solution (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (15 mL) and ethyl acetate (30 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 15 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (4:1 hexanes–ethyl acetate initially, grading to 2:1 hexanes–ethyl acetate, then 1:1 hexanes–ethyl acetate) to afford isoquinolyl alcohol **158** (estrone series) as a white solid (10.0 mg, 60%), and, separately, recovered ketone **156** (4.0 mg, 35%).

Trifluoroacetic anhydride (17.0 μL, 121 μmol, 5 equiv) was added dropwise to an ice-cooled solution of isoquinolyl alcohol **158** (10.0 mg, 24.2 μmol, 1 equiv), pyridine (19.0 μL, 242 μmol, 10 equiv) and 4-dimethylaminopyridine (1.5 mg, 12.1 μmol, 0.5 equiv) in dichloromethane (1.5 mL). After 10 min, the ice bath was removed and the reaction flask was allowed to warm to 23 ºC. After 20 min, the reaction mixture was partitioned between aqueous potassium phosphate buffer solution (pH 7.0, 0.2 M, 10 mL) and ethyl acetate (20 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on silica gel (5:1 hexanes–ethyl acetate initially, grading to 3:1 hexanes–ethyl acetate) to provide the intermediate trifluoroacetate ester as a pale yellow oil.

Benzene (ca. 1.0 mL) was added, and the resulting solution was transferred by cannula to a capped 10-mL microwave vessel (CEM Corporation, cat. #908035, cap affixed by crimping). The vessel was placed in a water bath at 23 ºC and volatiles were removed in vacuo through a 22-gauge needle in order to effect azeotropic drying. Benzene (0.40 mL) was added to the oily residue. To the resulting solution was added a solution of 2,2'-azobisisobutyronitrile (6.0 mg, 36 μmol, 1.5 equiv) in benzene (80 μL). The reaction mixture was degassed by sparging for 10 min with a slow stream of argon gas through a 22-gauge stainless steel needle. Tributyltin hydride (33.0 μL, 121 μmol, 5.0 equiv) was added. The vessel cap was sealed with Teflon® tape and then Parafilm®. After sealing, the vessel was placed in an oil bath preheated to 100 ºC. After 1 h, the oil

bath was removed and the reaction flask was allowed to cool to 23 ºC. The reaction mixture was directly purified by flash-column chromatography on silica gel (8:1 hexanes–ethyl acetate initially, grading to 4:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate) to furnish isoquinolyl estrone (**164**) as a white solid (7.7 mg, 80% over two steps).

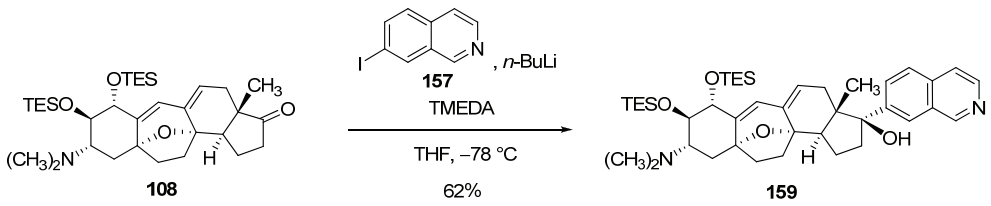
^{1}H NMR: (500 MHz, $CDCl_3$)	9.23 (s, 1H), 8.48 (d, 1H, *J* = 5.9 Hz), 7.81 (s, 1H), 7.75 (d, 1H, *J* = 8.8 Hz), 7.63 (d, 1H, *J* = 1.5 Hz), 7.62 (dd, 1H, *J* = 10.6, 1.0 Hz), 7.20 (d, 1H, *J* = 8.8 Hz), 6.70 (dd, 1H, *J* = 8.8, 2.4 Hz), 6.65 (s, 1H), 3.78 (s, 3H), 2.99 (app t, 1H, *J* = 9.8 Hz), 2.94–2.85 (m, 2H), 2.36–2.26 (m, 2H), 2.17–2.06 (m, 1H), 2.04–1.92 (m, 2H), 1.74 (d, 1H, *J* = 12.2 Hz), 1.70–1.61 (m, 1H), 1.61–1.51 (m, 2H), 1.50–1.40 (m, 2H), 1.36 (dd, 1H, *J* = 15.1, 7.3 Hz), 1.32–1.28 (m, 1H), 0.92 (app t, 1H, *J* = 7.3 Hz), 0.54 (s, 3H);
^{13}C NMR : (126 MHz, $CDCl_3$)	157.4, 152.3, 142.3, 140.7, 138.0, 134.6, 132.7, 132.4, 128.6, 126.3, 126.1, 125.5, 120.1, 113.8, 111.4, 57.2, 55.3, 55.2, 45.1, 44.0, 39.3, 37.8, 29.9, 27.8, 26.4, 26.2, 24.3, 12.9;
FTIR, cm^{-1}:	2957 (s), 2926 (s), 2872 (m), 1454 (m), 1387 (m), 1370

(thin film) (m).

HRMS:	Calcd for $(C_{28}H_{31}NO+H)^+$	398.2478
(ESI)	Found	398.2468

TLC R_f = 0.15 (UV, *p*-anisaldehyde)

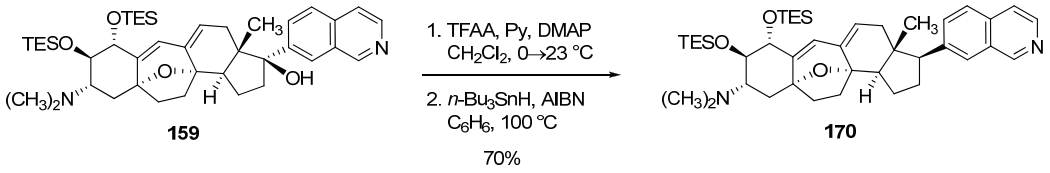
(4:1 hexanes–ethyl acetate)



Isoquinolyl Alcohol **159** (Cortistatin A Series).

A solution of *n*-butyllithium in hexanes (2.50 M, 232 μL, 0.578 mmol, 5 equiv) was added dropwise to a solution of 7-iodoisoquinoline (**157**) (148 mg, 0.578 mmol, 5 equiv) in tetrahydrofuran (4.5 mL) at –78 ºC, producing a dark red solution. After 30 min, *N,N,N',N'*-tetramethylethylenediamine (261 μL, 1.74 mmol, 15 equiv) was added. After 10 min, a solution of bistriethylsilyl ether ketone **108** (68 mg, 0.116 mmol, 1 equiv) in tetrahydrofuran (0.7 mL) was added via cannula. The flask containing dimethylamino ketone **108** (cortistatin A series) was rinsed with tetrahydrofuran (2 × 0.3 mL), and the rinses were added to the reaction mixture. After 30 min, saturated aqueous sodium bicarbonate solution (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (15 mL) and ethyl acetate (30 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 15 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate initially, grading to 4:1 then 1:2 hexanes–ethyl acetate) to afford isoquinolyl alcohol **159** (cortistatin A series) as a pale yellow oil (52 mg, 62%), and, separately, recovered dimethylamino ketone **108** (cortistatin A series) (23 mg, 34%).

^{1}H NMR: (500 MHz, $CDCl_3$)	9.21 (s, 1H), 8.48 (d, 1H, *J* = 6.0 Hz), 7.93 (br s, 1H), 7.86 (d, 1H, *J* = 7.8 Hz), 7.75 (d, 1H, *J* = 8.2 Hz), 7.60 (d, 1H, *J* = 5.5 Hz), 5.90 (d, 1H, *J* = 1.8 Hz), 5.15 (dd, 1H, *J* = 5.0, 2.3 Hz), 3.94 (d, 1H, *J* = 7.8 Hz), 3.41 (app t, 1H, *J* = 7.8 Hz), 2.62 (ddd, 1H, *J* = 14.2, 9.6, 4.6 Hz), 2.50–2.39 (m, 2H), 2.39–2.26 (m, 2H), 2.20 (s, 6H), 2.19–2.02 (m, 3H), 1.95–1.72 (m, 4H), 1.67–1.57 (m, 2H), 1.17 (s, 3H), 0.95–0.89 (m, 18H), 0.66–0.55 (m, 12H).	
^{13}C NMR : (126 MHz, $CDCl_3$)	153.1, 145.7, 143.2, 142.6, 139.4, 135.0, 130.6, 128.3, 125.8, 125.4, 121.1, 120.5, 120.2, 85.8, 82.1, 79.6, 76.3, 75.5, 64.9, 47.9, 46.2, 41.5, 39.3, 38.9, 35.7, 31.6, 29.4, 20.9, 17.6, 7.3, 7.2, 5.6, 5.3.	
FTIR, cm^{-1}: (thin film)	3391 (br), 2924 (s), 2878 (m), 1782 (s), 1624 (s), 1458 (s), 1244 (m).	
HRMS:	Calcd for $(C_{42}H_{64}N_2O_4Si_2+H)^+$	717.4477
(ESI)	Found	717.4480
TLC	R_f = 0.13 (UV, *p*-anisaldehyde)	
(1:2 hexanes–ethyl acetate)		



Cortistatin A Bis(triethylsilyl) Ether (**170**).

Trifluoroacetic anhydride (48 μL, 348 μmol, 5 equiv) was added dropwise to an ice-cooled solution of isoquinolyl alcohol (cortistatin A series) **159** (50 mg, 69.6 μmol, 1 equiv), pyridine (55 μL, 696 μmol, 10 equiv) and 4-dimethylaminopyridine (4.3 mg, 34.8 μmol, 0.5 equiv) in dichloromethane (7 mL). After 10 min, the ice bath was removed and the reaction flask was allowed to warm to 23 ºC. After 20 min, the reaction mixture was partitioned between aqueous potassium phosphate buffer solution (pH 7.0, 0.2 M, 20 mL) and ethyl acetate (30 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 20 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (2:1 hexanes–ethyl acetate initially, grading to 1:1 hexanes–ethyl acetate) to provide the intermediate trifluoroacetate ester as a pale yellow oil.

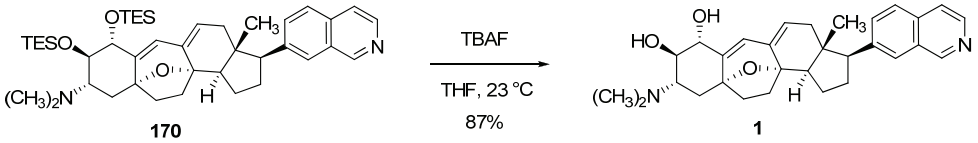
Benzene (1 mL) was added to the oily residue and volatiles were removed in vacuo through a 22-gauge needle in order to effect azeotropic drying. A second portion of benzene (1 mL) was added, and the volatiles were again removed. Benzene (1.2 mL) was added to the concentrate. To the resulting solution was added a solution of 2,2'-azobisisobutyronitrile (34 mg, 209 μmol, 3 equiv) in benzene (0.5 mL) followed by

tributyltin hydride (150 μL, 557 μmol, 8 equiv). The reaction mixture was degassed by sparging for 20 min with a slow stream of argon gas through a 22-gauge stainless steel needle. The flask was capped with a glass stopper under argon and the stopped flask was sealed with Teflon® tape and then Parafilm®. After sealing, the reaction flask was placed in an oil bath preheated to 100 ºC. After 2 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. The product solution was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate initially, grading to 4:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate) to afford cortistatin A bis(triethylsilyl) ether (**170**) as a pale yellow oil (34 mg, 70% over two steps).

^{1}H NMR: (500 MHz, $CDCl_3$) 9.23 (s, 1H), 8.49 (d, 1H, *J* = 5.4 Hz), 7.79 (s, 1H), 7.76 (d, 1H, *J* = 8.3 Hz), 7.63 (d, 1H, *J* = 5.4 Hz), 7.61–7.56 (dd, 1H, *J* = 8.5, 1.5 Hz, 1H), 6.03 (d, 1H, *J* = 1.5 Hz), 5.35 (dd, 1H, *J* = 4.9, 2.4 Hz), 3.99 (d, 1H, *J* = 7.8 Hz), 3.50 (app t, 1H, *J* = 7.8 Hz), 3.14 (app t, 1H, *J* = 9.8 Hz), 2.56–2.41 (m, 2H), 2.41–2.28 (m, 2H), 2.23 (s, 6H), 2.28–2.21 (m, 1H), 2.21–2.14 (m, 2H), 2.12–1.99 (m, 1H), 1.99–1.89 (m, 2H), 1.89–1.80 (m, 1H), 1.75–1.68 (m, 1H), 1.68–1.59 (m, 2H), 1.01–0.87 (m, 18H), 0.71–0.57 (m, 12H), 0.55 (s, 3H).

^{13}C NMR : 152.4, 142.7, 142.5, 140.6, 140.1, 134.7, 132.0, 128.6,

(126 MHz, $CDCl_3$)	126.3, 125.8, 120.4, 120.2, 120.1, 81.4, 79.3, 76.1, 75.4, 64.7, 57.0, 51.7, 44.8, 41.3, 40.1, 38.8, 30.8, 29.1, 26.5, 20.6, 15.2, 7.1, 7.0, 5.3, 5.1.	
FTIR, cm^{-1}: (thin film)	2957 (s), 2874 (m), 1622 (m), 1508 (s), 1452 (s), 1368 (m).	
HRMS: (ESI)	Calcd for $(C_{42}H_{64}N_2O_3Si_2+H)^+$ found	699.4372 699.4355
TLC (1:1 hexanes–ethyl acetate)	R_f = 0.20 (UV, *p*-anisaldehyde)	



Cortistatin A (**1**).

A solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (1.0 M, 291 μL, 291 μmol, 6 equiv) was added to a solution of cortistatin A bis(triethylsilyl) ether (**170**) (34 mg, 48.5 μmol, 1 equiv) in tetrahydrofuran (2.4 mL) at 23 ºC. After 20 min, the reaction mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was further extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (20 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (5:1 ethyl acetate–methanol initially, grading to 2:1 ethyl acetate–methanol, then 1:1 ethyl acetate–methanol). Fractions containing cortistatin A (**1**) were collected and the pooled fractions were concentrated. The residue was further purified by flash-column chromatography on Sephadex® LH-20 resin (methanol) to afford cortistatin A (**1**) as a white solid (20 mg, 87%, >85% purity by ^{1}H NMR analysis).

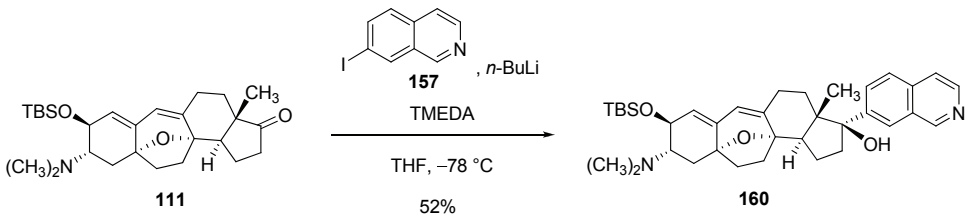
Further purification could be achieved by HPLC using an Agilent Eclipse XDB-C8 column (9.4 mm × 250 mm, UV detection at 245 nm, solvent A: water containing 0.1% formic acid, solvent B: acetonitrile containing 0.1% formic acid, gradient elution 5→25% B over 60 min, flow rate: 3 mL/min). Fractions eluting at 28–31 min were collected and concentrated. To the residue was added saturated aqueous sodium

bicarbonate solution (10 mL). The aqueous solution was extracted with dichloromethane (4 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was then purified by flash column chromatography on Sephadex® LH-20 resin (methanol) to afford cortistatin A (**1**) as a white solid. In a typical HPLC purification sequence submission of a 2.0-mg sample provided 1.3 mg of cortistatin A (**1**) of >95% purity.

^{1}H NMR: (500 MHz, $CDCl_3$)	9.22 (br s, 1H), 8.49 (d, 1H, *J* = 5.4 Hz), 7.79 (s, 1H), 7.76 (d, 1H, *J* = 8.8 Hz), 7.63 (d, 1H, *J* = 5.4 Hz), 7.59 (dd, 1H, *J* = 8.5, 1.6 Hz), 6.25 (d, 1H, *J* = 2.4 Hz), 5.44 (dd, 1H, *J* = 5.2, 2.2 Hz), 4.09 (d, 1H, *J* = 9.3 Hz), 3.33 (app t, 1H, *J* = 9.8 Hz), 3.15 (app t, 1H, *J* = 9.9 Hz), 2.51 (dd, 1H, *J* = 11.5, 8.5 Hz), 2.42 (ddd, 1H, *J* = 12.7, 9.6, 3.1 Hz), 2.41–2.32 (m, 2H), 2.30 (s, 6H), 2.29–2.23 (m, 1H), 2.22–2.14 (m, 2H), 2.10–2.01 (m, 1H), 1.96 (dd, 1H, *J* = 17.6, 5.4 Hz), 1.95–1.89 (m, 1H), 1.89–1.84 (m, 2H), 1.83–1.75 (m, 1H), 1.66 (app td, 1H, *J* = 10.5, 8.5 Hz), 0.54 (s, 3H).
^{13}C NMR : (126 MHz, $CDCl_3$)	152.3, 142.6, 140.0, 139.9, 139.6, 134.7, 132.0, 128.6, 126.3, 125.8, 121.4, 120.1, 119.4, 81.9, 79.5, 74.1, 73.7, 62.2, 56.9, 51.7, 44.8, 40.1, 40.0, 39.7, 30.6, 29.0, 26.4,

20.5, 15.2.

FTIR, cm^{-1}: (thin film)	3464 (br), 2928 (s), 2860 (m), 1627 (m), 1450 (m), 1375 (s), 1263 (s).	
HRMS: (ESI)	Calcd for $(C_{30}H_{36}N_2O_3+H)^+$	473.2799
	found	473.2796
TLC (methanol)	R_f = 0.20 (UV, *p*-anisaldehyde)	
Optical Rotation	$[\alpha]_D^{23}$ = +31.1° (c = 0.090 in methanol); lit.[20]: $[\alpha]_D^{20}$ = +30.1° (c = 0.56 in methanol)	



Isoquinolyl Alcohol **160** (Cortistatin L Series).

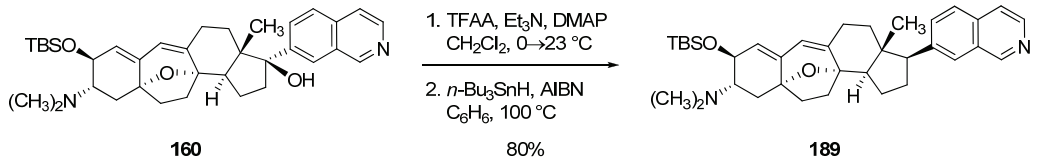
A solution of *n*-butyllithium in hexanes (2.50 M, 62 μL, 153 μmol, 5 equiv) was added dropwise to a solution of 7-iodoisoquinoline (**157**) (39 mg, 153 μmol, 5 equiv) in tetrahydrofuran (1.5 mL) at −78 ºC, producing a dark red solution. After 30 min, *N,N,N',N'*-tetramethylethylenediamine (69 μL, 459 μmol, 15 equiv) was added. After 10 min, a solution of dimethylamino ketone **111** (cortistatin L series) (14 mg, 30.6 μmol, 1 equiv) in tetrahydrofuran (0.3 mL) was added via cannula. The flask containing dimethylamino ketone **111** (cortistatin L series) was rinsed with tetrahydrofuran (2 × 0.1 mL), and the rinses were added to the reaction mixture. After 30 min, saturated aqueous sodium bicarbonate solution (0.5 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (10 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (90:9:1 hexanes–acetone–triethylamine initially, grading to 80:19:1 then 66:33:1 hexanes–acetone–triethylamine) to afford isoquinolyl alcohol **160** (cortistatin L

series) as a pale yellow solid (9.3 mg, 52%) and, separately, recovered dimethylamino ketone **111** (cortistatin L series) (5.6 mg, 40%).

^{1}H NMR: (500 MHz, $CDCl_3$)	9.22 (s, 1H), 8.50 (d, 1H, *J* = 5.9 Hz), 7.88 (br s, 1H), 7.83 (d, 1H, *J* = 8.3 Hz), 7.74 (d, 1H, *J* = 8.3 Hz), 7.61 (d, 1H, *J* = 5.9 Hz), 5.51 (d, 1H, *J* = 2.0 Hz), 5.02 (d, 1H, *J* = 2.4 Hz), 4.19 (d, 1H, *J* = 8.3 Hz), 2.68–2.53 (m, 2H), 2.42–2.33 (m, 1H), 2.32–2.24 (m, 2H), 2.27 (s, 6H), 2.21–1.97 (m, 5H), 1.96–1.76 (m, 4H), 1.55–1.49 (m, 1H), 1.21 (s, 3H), 0.86 (s, 9H), 0.54 (app td, 1H, *J* = 13.2, 4.9 Hz), 0.05 (s, 3H), 0.03 (s, 3H).
^{13}C NMR : (126 MHz, $CDCl_3$)	153.0, 146.0, 144.7, 143.1, 139.8, 134.8, 130.5, 127.9, 125.4, 125.3, 123.3, 119.9, 119.3, 85.7, 83.7, 79.3, 69.2, 65.6, 47.7, 47.2, 41.0, 38.5, 37.8, 33.2, 32.6, 28.4, 25.9, 25.9, 20.5, 18.3, 14.6, –4.2, –4.7.
FTIR, cm^{-1}: (thin film)	3264 (br), 2930 (s), 2857 (m), 1455 (m), 1250 (s).

HRMS:	Calcd for $(C_{36}H_{50}N_2O_3Si+H)^+$	587.3664
(ESI)	Found	587.3652

TLC R_f = 0.35 (UV, *p*-anisaldehyde)
(66:33:1 hexane–acetone–triethylamine)



160 **189**

Cortistatin L *tert*-Butyldimethylsilyl Ether (**189**).

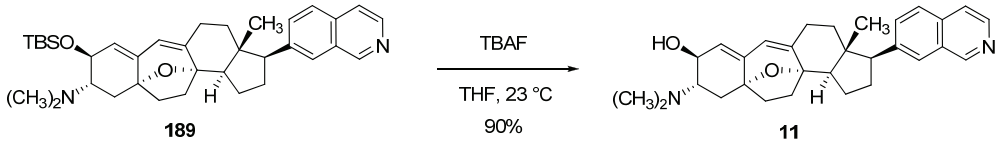
Trifluoroacetic anhydride (6.1 μL, 44 μmol, 5.0 equiv) was added dropwise to an ice-cooled solution of isoquinolyl alcohol (cortistatin L series) **160** (5.2 mg, 8.8 μmol, 1 equiv), triethylamine (12 μL, 88 μmol, 10 equiv) and 4-dimethylaminopyridine (0.54 mg, 4.4 μmol, 0.50 equiv) in dichloromethane (1.7 mL). After 5 min, the ice bath was removed and the reaction flask was allowed to warm to 23 ºC. After 10 min, the reaction mixture was partitioned between aqueous potassium phosphate buffer solution (pH 7.0, 0.2 M, 10 mL) and ethyl acetate (15 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (88:11:1 hexanes–acetone–triethylamine) to provide the intermediate trifluoroacetate ester as a pale yellow oil.

Benzene (ca. 1.5 mL) was added, and the resulting solution was transferred by cannula to a a capped10-mL microwave vessel (CEM Corporation, cat. #908035, cap affixed by crimping). The vessel was placed in a water bath at 23 ºC and volatiles were removed in vacuo through a 22-gauge needle in order to effect azeotropic drying. Benzene (0.80 mL) was added to the oily residue. To the resulting solution was added a solution of 2,2'-azobisisobutyronitrile (4.4 mg, 26 μmol, 3.0 equiv) in benzene (80 μL) followed by tributyltin hydride (14 μL, 52 μmol, 6.0 equiv). The reaction mixture was

degassed by sparging for 20 min with a slow stream of argon gas through a 22-gauge stainless steel needle. The vessel cap was sealed with Teflon® tape and then Parafilm®. After sealing, the vessel was placed in an oil bath preheated to 100 ºC. After 1 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. The reaction mixture was transferred by pipette to a round-bottom flask and the product solution was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (90:9:1 hexanes–acetone–triethylamine initially, grading to 80:19:1 hexanes–acetone–triethylamine) to furnish cortistatin L *tert*-butyldimethylsilyl ether (**189**) as a pale yellow oil (4.0 mg, 80% over two steps).

^{1}H NMR: (500 MHz, $CDCl_3$)	9.22 (s, 1H), 8.48 (d, 1H, *J* = 5.9 Hz), 7.78 (s, 1H), 7.75 (d, 1H, *J* = 9.0 Hz), 7.62 (d, 1H, *J* = 5.9 Hz), 7.57 (dd, 1H, *J* = 8.8, 1.5 Hz), 5.72 (d, 1H, *J* = 1.5 Hz), 5.13 (d, 1H, *J* = 2.4 Hz), 4.26 (d, 1H, *J* = 7.8 Hz), 3.00 (app t, 1H, *J* = 10.0 Hz), 2.69–2.55 (m, 1H), 2.29 (s, 6H), 2.37–2.23 (m, 3H), 2.20–2.03 (m, 3H), 2.03–1.93 (m, 1H), 1.93–1.76 (m, 5H), 1.67–1.56 (m, 2H), 1.52 (app td, 1H, *J* = 12.7, 5.9 Hz), 0.90 (s, 9H), 0.60 (s, 3H), 0.09 (s, 3H), 0.09 (s, 3H).
^{13}C NMR : (126 MHz, $CDCl_3$)	152.4, 146.6, 142.5, 140.2, 139.9, 134.7, 132.3, 128.6, 126.4, 125.7, 123.0, 120.1, 119.4, 83.4, 79.3, 69.4, 65.8,

	57.5, 53.5, 45.3, 41.0, 37.8, 37.2, 32.7, 32.5, 28.5, 26.0, 26.0, 20.7, 18.3, 12.8, –4.1, –4.7.	
FTIR, cm^{-1}: (thin film)	3393 (br), 2936 (m), 2857 (m), 1792 (m), 1724 (s), 1464 (m), 1256 (m).	
HRMS: (ESI)	Calcd for $(C_{36}H_{50}N_2O_2Si+H)^+$	571.3714
	Found	571.3713
TLC (66:33:1 hexanes–acetone–triethylamine)	R_f = 0.55 (UV, *p*-anisaldehyde)	



Cortistatin L (**11**).

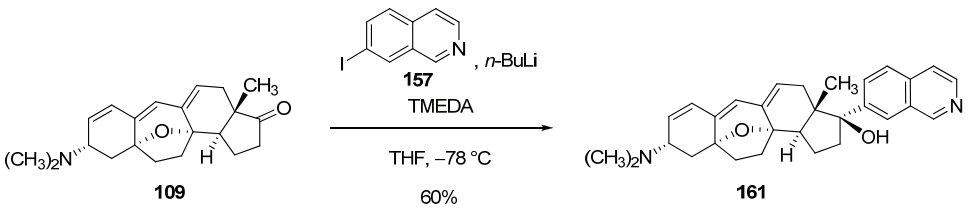
A solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (1.0 M, 62 µL, 62 µmol, 10 equiv) was added to a solution of cortistatin L *tert*-butyldimethylsilyl ether **189** (3.5 mg, 6.1 µmol, 1 equiv) in tetrahydrofuran (0.30 mL) at 23 ºC. After 5 h, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution (5 mL) and ethyl acetate (10 mL). The layers were separated. The aqueous layer was further extracted with ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 2:1 methanol–ethyl acetate) to furnish cortistatin L (**11**) as a white solid (2.5 mg, 90%, >90% purity as judged by ^{1}H NMR analysis).

Further purification could be achieved by HPLC using an Agilent Eclipse XDB-C8 column (9.4 mm × 250 mm, UV detection at 245 nm, solvent A: water containing 0.1% formic acid, solvent B: acetonitrile containing 0.1% formic acid, gradient elution 5→25% B over 60 min, flow rate: 3 mL/min). Fractions eluting at 27–30 min were collected and concentrated. To the residue was added saturated aqueous sodium bicarbonate solution (10 mL). The aqueous solution was extracted with dichloromethane (4 × 10 mL). The combined organic layers were washed with saturated aqueous sodium

chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (1:1 methanol–ethyl acetate) to afford cortistatin L (**11**) as a white solid. In a typical HPLC purification sequence submission of a 2.0-mg sample provided 1.0 mg of cortistatin L (**11**) of >95% purity.

^{1}H NMR: (600 MHz, $CDCl_3$)	9.22 (s, 1H), 8.48 (d, 1H, *J* = 5.6 Hz), 7.78 (s, 1H), 7.75 (d, 1H, *J* = 8.5 Hz), 7.62 (d, 1H, *J* = 5.6 Hz), 7.50 (dd, 1H, *J* = 8.5, 1.5 Hz), 5.75 (d, 1H, *J* = 1.8 Hz), 5.35 (d, 1H, *J* = 2.1 Hz), 4.23 (d, 1H, *J* = 9.1 Hz), 3.13 (br s, 1H), 3.00 (app t, 1H, *J* = 9.8 Hz), 2.59 (dd, 1H, *J* = 11.8, 8.8 Hz), 2.31 (s, 6H), 2.41–2.28 (m, 3H), 2.28–2.22 (m, 1H), 2.20–2.13 (m, 1H), 2.12–2.04 (m, 2H), 2.02–1.94 (m, 1H), 1.94–1.89 (m, 1H), 1.89–1.76 (m, 4H), 1.62 (dd, 1H, *J* = 12.5, 5.0 Hz), 1.51 (app td, 1H, *J* = 12.5, 5.0 Hz), 0.60 (s, 3H).
^{13}C NMR : (126 MHz, $CDCl_3$)	152.4, 146.8, 142.6, 140.9, 139.8, 134.7, 132.2, 128.6, 126.4, 125.7, 120.2, 120.1, 119.4, 83.7, 79.7, 67.8, 66.1, 57.5, 53.5, 45.2, 40.5, 38.5, 37.2, 32.5, 30.2, 28.5, 25.9, 20.7, 12.8.
FTIR, cm^{-1}:	3404 (br), 2932 (s), 2857 (m), 1792 (m), 1624 (s), 1456

(thin film)	(s), 1254 (m).	
HRMS:	Calcd for $(C_{30}H_{36}N_2O_2+H)^+$	457.2850
(ESI)	Found	457.2852
TLC	R_f = 0.29 (UV, *p*-anisaldehyde)	
(methanol)		
Optical Rotation	$[\alpha]_D^{23}$ = –23.8º (c = 0.021 in chloroform)	
	lit.[21]: $[\alpha]_D^{20}$ = –28.9º (c = 0.20 in chloroform)	

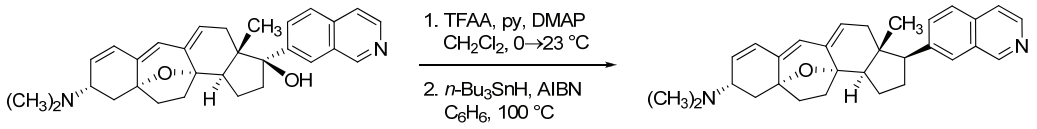


Isoquinolyl Alcohol **161** (Cortistatin J Series).

A solution of *n*-butyllithium in hexanes (2.50 M, 117 μL, 292 μmol, 5 equiv) was added dropwise to a solution of 7-iodoisoquinoline (**157**) (75 mg, 292 μmol, 5 equiv) in tetrahydrofuran (2.4 mL) at –78 ºC, producing a dark red solution. After 30 min, *N,N,N',N'*-tetramethylethylenediamine (132 μL, 876 μmol, 15 equiv) was added. After 10 min, a solution of dimethylamino ketone **109** (cortistatin J series) (19 mg, 58.4 μmol, 1 equiv) in tetrahydrofuran (0.3 mL) was added via cannula. The flask containing dimethylamino ketone **109** (cortistatin J series) was rinsed with tetrahydrofuran (2 × 0.1 mL), and the rinses were added to the reaction mixture. After 1 h, saturated aqueous sodium bicarbonate solution (0.5 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (15 mL) and ethyl acetate (20 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 15 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (15 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 5:1 ethyl acetate–methanol, then 2:1 ethyl acetate–methanol, then 1:1 ethyl acetate–methanol, then 1:2 ethyl acetate–methanol) to

afford isoquinolyl alcohol **161** (cortistatin J series) as a pale yellow solid (16 mg, 60%) and, separately, recovered dimethylamino ketone **109** (cortistatin J series) (6.7 mg, 35%).

^{1}H NMR: (500 MHz, $CDCl_3$)	9.22 (s, 1H), 8.50 (d, 1H, *J* = 5.7 Hz), 7.94 (br s, 1H), 7.86 (d, 1H, *J* = 7.8 Hz), 7.75 (d, 1H, *J* = 8.7 Hz), 7.61 (d, 1H, *J* = 5.7 Hz), 6.02 (dd, 1H, *J* = 9.8, 2.5 Hz), 5.76 (d, 1H, *J* = 9.8 Hz), 5.69 (s, 1H), 5.22 (dd, 1H, *J* = 5.3, 2.7 Hz), 3.44 (d, 1H, *J* = 9.4 Hz), 2.63 (ddd, 1H, *J* = 14.3, 9.7, 4.7 Hz), 2.52 (dd, 1H, *J* = 11.0, 8.9 Hz), 2.45–2.36 (m, 1H), 2.33 (dd, 1H, *J* = 13.5, 6.0 Hz), 2.29 (s, 6H), 2.23–2.06 (m, 3H), 2.06–2.00 (m, 1H), 2.00–1.80 (m, 4H), 1.69 (app td, 1H, *J* = 11.0, 7.4 Hz), 1.63–1.53 (m, 1H), 1.19 (s, 3H).
^{13}C NMR : (126 MHz, $CDCl_3$)	152.9, 145.3, 143.1, 139.8, 139.4, 134.8, 131.9, 130.3, 128.0, 127.3, 125.6, 125.2, 122.4, 120.9, 119.9, 85.5, 82.7, 78.9, 60.4, 47.6, 45.8, 40.4, 38.9, 37.9, 35.7, 31.0, 30.9, 20.7, 17.4.
FTIR, cm^{-1}: (thin film)	3385 (br), 2942 (m), 1788 (m), 1624 (s), 1464 (m), 1157 (s).
HRMS: (ESI)	Calcd for $(C_{30}H_{34}N_2O_2+H)^+$ 455.2692 Found 455.2707
TLC (methanol)	R_f = 0.22 (UV, *p*-anisaldehyde)



Cortistatin J (**9**).

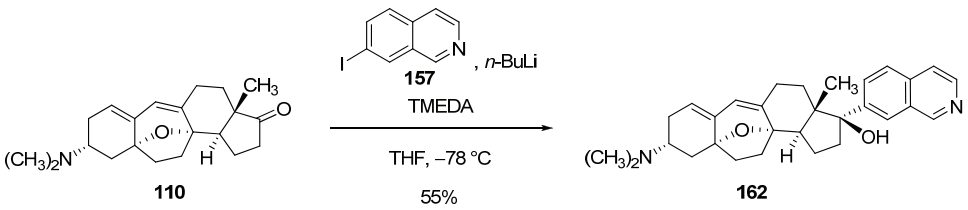
Trifluoroacetic anhydride (6.1 μL, 44 μmol, 5.0 equiv) was added dropwise to an ice-cooled solution of isoquinolyl alcohol **161** (cortistatin J series) (4.0 mg, 8.8 μmol, 1 equiv), pyridine (7.2 μL, 88 μmol, 10 equiv) and 4-dimethylaminopyridine (0.54 mg, 4.4 μmol, 0.50 equiv) in dichloromethane (1.7 mL) at 0 ºC. After 5 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 20 min, the reaction mixture was partitioned between aqueous potassium phosphate buffer solution (pH 7.0, 0.2 M, 10 mL) and ethyl acetate (10 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 2:1 methanol–ethyl acetate) to provide the intermediate trifluoroacetate ester as a pale yellow oil.

Benzene (ca. 1.5 mL) was added, and the resulting solution was transferred by cannula to a capped 10-mL microwave vessel (CEM Corporation, cat. #908035, cap affixed by crimping). The vessel was placed in a water bath at 23 ºC and volatiles were removed in vacuo through a 22-gauge needle in order to effect azeotropic drying. Benzene (0.80 mL) was added to the oily residue. To the resulting solution was added a solution of 2,2'-azobisisobutyronitrile (4.4 mg, 26 μmol, 3.0 equiv) in benzene (80 μL) followed by tributyltin hydride (14 μL, 52 μmol, 6.0 equiv). The reaction mixture was

degassed by sparging for 20 min with a slow stream of argon gas through a 22-gauge stainless steel needle. The vessel cap was sealed with Teflon® tape and then Parafilm®. After sealing, the vessel was placed in an oil bath preheated to 100 ºC. After 1 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. The reaction mixture was transferred by pipette to a round-bottom flask and the product solution was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 2:1 methanol–ethyl acetate) to furnish cortistatin J (**9**) as a white solid (2.5 mg, 65% over two steps, >90% purity as judged by ^{1}H NMR analysis).

Further purification could be achieved by HPLC using an Agilent Eclipse XDB-C8 column (9.4 mm × 250 mm, UV detection at 245 nm, solvent A: water containing 0.1% formic acid, solvent B: acetonitrile containing 0.1% formic acid, gradient elution 5→25% B over 45 min, flow rate: 3 mL/min). Fractions eluting at 22–26 min were collected and concentrated. To the residue was added saturated aqueous sodium bicarbonate solution (10 mL). The aqueous solution was extracted with dichloromethane (4 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was then purified by flash column chromatography on Davisil® silica gel (1:1 methanol–ethyl acetate) to afford cortistatin J (**9**) as a white solid. In a typical HPLC purification sequence submission of a 2.0-mg sample provided 1.0 mg of cortistatin J (**9**) of >95% purity.

^{1}H NMR: (500 MHz, $CDCl_3$)	9.23 (s, 1H), 8.49 (d, 1H, *J* = 5.9 Hz), 7.80 (s, 1H), 7.76 (d, 1H, *J* = 8.8 Hz), 7.63 (d, 1H, *J* = 5.9 Hz), 7.59 (dd, 1H, *J* = 8.3, 1.5 Hz), 6.09 (dd, 1H, *J* = 10.0, 2.7 Hz), 5.84 (s, 1H), 5.81 (d, 1H, *J* = 9.8 Hz), 5.42 (dd, 1H, *J* = 5.1, 2.7 Hz), 3.45 (d, 1H, *J* = 10.7 Hz), 3.17 (app t, 1H, *J* = 10.0 Hz), 2.56 (dd, 1H, *J* = 11.5, 8.5 Hz), 2.41 (d, 1H, *J* = 19.0 Hz), 2.32 (s, 6H), 2.36–2.26 (m, 2H), 2.25–2.14 (m, 1H), 2.12–1.96 (m, 4H), 1.95–1.84 (m, 2H), 1.81–1.65 (m, 2H), 0.58 (s, 3H).	
^{13}C NMR : (126 MHz, $CDCl_3$)	152.4, 142.6, 141.2, 140.0, 139.8, 134.7, 132.2, 132.0, 128.6, 127.4, 126.3, 125.8, 121.8, 121.1, 120.1, 82.3, 79.0, 60.5, 57.0, 51.7, 44.9, 40.6, 40.3, 38.0, 31.1, 30.5, 26.5, 20.6, 15.4.	
FTIR, cm^{-1}: (thin film)	2933 (s), 1716 (s), 1647 (s), 1450 (m), 1366 (m), 1277 (s).	
HRMS:	Calcd for $(C_{30}H_{34}N_2O+H)^+$	439.2744
(ESI)	Found	439.2743
TLC (methanol)	R_f = 0.32 (UV, *p*-anisaldehyde)	
Optical Rotation	$[\alpha]_D^{23}$ = –51.7º (c = 0.041 in chloroform)	
	lit. [21]: $[\alpha]_D^{20}$ = –54.0º (c = 0.26 in chloroform)	

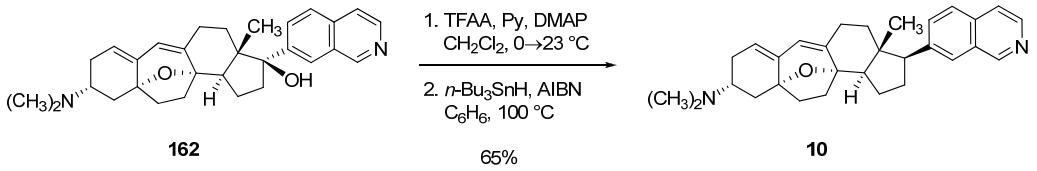


Isoquinolyl Alcohol **162** (Cortistatin K Series).

A solution of *n*-butyllithium in hexanes (2.50 M, 92 µl, 229 µmol, 5 equiv) was added dropwise to a solution of 7-iodoisoquinoline (**157**) (59 mg, 229 µmol, 5 equiv) in tetrahydrofuran (1.8 mL) at –78 ºC, producing a dark red solution. After 30 min, *N,N,N',N'*-tetramethylethylenediamine (103 µL, 687 µmol, 15 equiv) was added. After 10 min, a solution of dimethylamino ketone **110** (cortistatin K series) (15 mg, 45.8 µmol, 1 equiv) in tetrahydrofuran (0.3 mL) was added via cannula. The flask containing dimethylamino ketone **110** (cortistatin K series) was rinsed with tetrahydrofuran (2 × 0.1 mL), and the rinses were added to the reaction mixture. After 1 h, saturated aqueous sodium bicarbonate solution (0.5 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (15 mL) and ethyl acetate (20 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 15 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (15 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 5:1 ethyl acetate–methanol, then 2:1 then 1:1 ethyl acetate–methanol) to afford isoquinolyl alcohol **162** (cortistatin K series) as a pale

yellow solid (11.5 mg, 55%), and separately, recovered dimethylamino ketone **110** (cortistatin K series) (6.0 mg, 40%).

^{1}H NMR: (500 MHz, $CDCl_3$)	9.23 (s, 1H), 8.50 (d, 1H, *J* = 5.9 Hz), 7.89 (br s, 1H), 7.83 (d, 1H, *J* = 8.5 Hz), 7.74 (d, 1H, *J* = 8.5 Hz), 7.60 (d, 1H, *J* = 5.6 Hz), 5.53 (d, 1H, *J* = 2.1 Hz), 5.17 (dd, 1H, *J* = 4.7, 2.6 Hz), 2.70–2.57 (m, 2H), 2.47–2.34 (m, 1H), 2.30 (s, 6H), 2.32–2.27 (m, 1H), 2.27–2.13 (m, 4H), 2.13–2.00 (m, 4H), 2.00–1.82 (m, 4H), 1.55–1.50 (m, 1H), 1.21 (s, 3H), 0.54 (app td, 1H, *J* = 13.2, 5.0 Hz).
^{13}C NMR : (126 MHz, $CDCl_3$)	153.0, 144.8, 144.4, 143.0, 139.7, 134.8, 130.5, 127.9, 125.4, 119.9, 119.5, 118.0, 85.7, 83.6, 79.2, 58.7, 47.8, 47.2, 41.0, 38.8, 38.5, 36.5, 33.6, 33.2, 28.3, 27.9, 20.6, 14.6.
FTIR, cm^{-1}: (thin film)	3234 (br), 2930 (s), 2859 (m), 1454 (m), 1279 (m).
HRMS: (ESI)	Calcd for $(C_{30}H_{36}N_2O_2+H)^+$ 457.2850 Found 457.2856
TLC (methanol)	R_f = 0.23 (UV, *p*-anisaldehyde)



Cortistatin K (**10**).

Trifluoroacetic anhydride (6.1 μL, 44 μmol, 5 equiv) was added dropwise to an ice-cooled solution of isoquinolyl alcohol (cortistatin K series) **162** (4.0 mg, 8.8 μmol, 1 equiv), pyridine (7.2 μL, 88 μmol, 10 equiv) and 4-dimethylaminopyridine (0.54 mg, 4.4 μmol, 0.50 equiv) in dichloromethane (1.7 mL). After 5 min, the ice bath was removed and the reaction flask was allowed to warm to 23 ºC. After 20 min, the reaction mixture was partitioned between aqueous potassium phosphate buffer solution (pH 7.0, 0.2 M, 10 mL) and ethyl acetate (10 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 1:1 methanol–ethyl acetate) to provide the intermediate trifluoroacetate ester as a pale yellow oil.

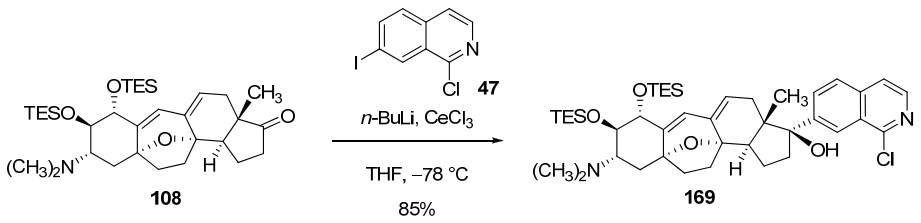
Benzene (ca. 1.0 mL) was added, and the resulting solution was transferred by cannula to a 10-mL microwave vessel (CEM Corporation, cat. #908035), to which a cap had been affixed by crimping. The vessel was placed in a water bath at 23 ºC and volatiles were removed in vacuo through a 22-gauge needle in order to effect azeotropic drying. Benzene (0.20 mL) was added to the oily residue. To the resulting solution was added a solution of 2,2'-azobisisobutyronitrile (4.4 mg, 26 μmol, 3.0 equiv) in benzene (80 μL) followed by tributyltin hydride (19 μL, 70.1 μmol, 8.0 equiv). The reaction

mixture was degassed by sparging for 20 min with a slow stream of argon gas through a 22-gauge stainless steel needle. The vessel cap was sealed with Teflon® tape and then Parafilm®. After sealing, the vessel was placed in an oil bath preheated to 100 ºC. After 2 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. The reaction mixture was transferred by pipette to a round-bottom flask and the product solution was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (ethyl acetate initially, grading to 5:1 ethyl acetate–methanol, then 1:1 ethyl acetate–methanol) to furnish cortistatin K (**10**) as a white solid (2.5 mg, 65% over two steps, >90% purity as judged by ^{1}H NMR analysis).

Further purification could be achieved by HPLC using an Agilent Eclipse XDB-C8 column (9.4 mm × 250 mm, UV detection at 245 nm, solvent A: water containing 0.1% formic acid, solvent B: acetonitrile containing 0.1% formic acid, gradient elution 5→25% B over 45 min, flow rate: 3 mL/min). Fractions eluting at 20–25 min were collected and concentrated. To the residue was added saturated aqueous sodium bicarbonate solution (10 mL). The aqueous solution was extracted with dichloromethane (4 × 10 mL). The combined organic layers were washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was then purified by flash column chromatography on Sephadex® LH-20 resin (methanol) to afford cortistatin K (**10**) as a white solid. In a typical HPLC purification sequence submission of a 2.0-mg sample provided 1.2 mg of cortistatin K (**10**) of >95% purity.

^{1}H NMR: 9.22 (s, 1H), 8.48 (d, 1H, J = 5.9 Hz), 7.79 (s, 1H), 7.75

(500 MHz, $CDCl_3$)	(d, 1H, J = 8.8 Hz), 7.62 (d, 1H, J = 5.9 Hz), 7.58 (d, 1H, J = 8.3 Hz), 5.74 (s, 1H), 5.27 (br s, 1H), 3.00 (app t, 1H, J = 9.8 Hz), 2.67 (app br s, 1H), 2.33 (s, 6H), 2.45–2.23 (m, 5H), 2.22–2.06 (m, 3H), 2.05–1.97 (m, 3H), 1.95–1.78 (m, 4H), 1.65–1.58 (m, 1H), 1.51 (app td, 1H, J = 12.9, 4.9 Hz), 0.60 (s, 3H).	
^{13}C NMR :	δ 152.4, 144.9, 142.5, 140.2, 140.0, 134.7, 132.3, 128.7,	
(100 MHz, $CDCl_3$)	126.4, 125.7, 120.1, 119.7, 117.7, 83.3, 79.3, 58.9, 57.5, 53.5, 45.3, 41.1, 38.9, 37.2, 36.6, 33.1, 28.4, 28.3, 26.0, 20.7, 12.8.	
FTIR, cm^{-1}:	2955 (s), 2930 (s), 2857 (m), 1599 (m), 1472 (m), 1371	
(thin film)	(s), 1254 (s).	
HRMS:	Calcd for $(C_{30}H_{36}N_2O+H)^+$	441.2900
(ESI)	Found	441.2892
TLC	R_f = 0.30 (UV, p-anisaldehyde)	
(methanol)		
Optical Rotation	$[\alpha]_D^{23}$ = –50.1° (c = 0.077 in chloroform);	
	lit. [21]: $[\alpha]_D^{20}$ = –47.1° (c = 0.32 in chloroform)	



1'-Chloro-Isoquinolyl Alcohol **169** (Cortistatin A Series).

To a flame-dried, 10-mL Schlenk flask fitted with a stirring bar was added anhydrous cerium(III) chloride powder (101 mg, 408 μmol, 10 equiv) in glovebox. The reaction flask was placed under high vacuum (0.5 mmHg) and heated in an oil bath at 90 ºC with vigorous stirring. After 2 h, the oil bath was removed. The reaction flask was back filled with Ar and cooled in an ice bath. Tetrahydrofuran (1.0 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The white suspension was stirred vigorously. After 16 h, a solution of 1-chloro-7-iodoisoquinoline (**47**) (65 mg, 224 μmol, 5.5 equiv) in tetrahydrofuran (0.25 mL) was added. The reaction flask was cooled to −78 ºC in a dry ice-acetone bath. A solution of *n*-butyllithium in hexanes (2.50 M, 82 μl, 204 μmol, 5 equiv) was added, producing a chartreuse suspension. After 30 min, a solution of dimethylamino ketone **108** (cortistatin A series) (24.0 mg, 40.8 μmol, 1 equiv) in tetrahydrofuran (0.25 mL) was added. After 30 min, saturated aqueous ammonium chloride solution (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (15 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered

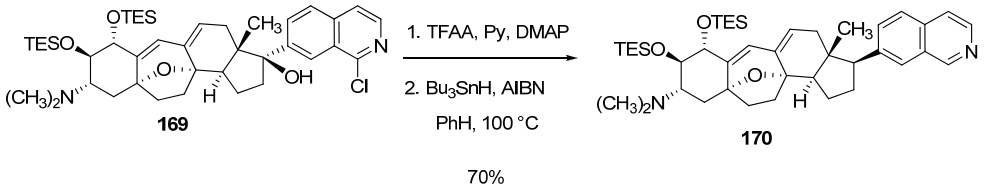
and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate initially, grading to 5:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate, finally 1:1 hexanes–ethyl acetate) to afford 1'-chloro-isoquinolyl alcohol **169** (cortistatin A series) as a pale yellow foam (26.0 mg, 85%).

^{1}H NMR: (500 MHz, $CDCl_3$)	8.37 (br s, 1H), 8.26 (d, 1H, *J* = 6.0 Hz), 7.86 (br d, 1H, *J* = 10.1 Hz), 7.77 (d, 1H, *J* = 9.2 Hz), 7.57 (d, 1H, *J* = 5.5 Hz), 5.91 (s, 1H), 5.16 (dd, 1H, *J* = 4.8, 2.5 Hz), 3.93 (d, 1H, *J* = 7.8 Hz), 3.40 (app t, 1H, *J* = 8.0 Hz), 2.63 (app td, 1H, *J* = 9.5, 4.8 Hz), 2.48–2.40 (m, 1H), 2.39–2.27 (m, 2H), 2.20 (s, 6H), 2.17–2.07 (m, 4H), 1.91 (dd, 1H, *J* = 17.9, 5.0 Hz), 1.87–1.74 (m, 2H), 1.67–1.58 (m, 1H), 1.51 (d, 1H, *J* = 17.9 Hz), 1.29–1.23 (m, 1H), 1.17 (s, 3H), 0.98–0.89 (m, 18H), 0.67–0.56 (m, 12H);
^{13}C NMR : (126 MHz, $CDCl_3$)	151.8, 146.8, 142.5, 141.5, 139.1, 136.7, 131.0, 126.3, 126.2, 124.0, 120.8, 120.2, 120.0, 85.7, 81.7, 79.3, 76.1, 75.3, 64.5, 47.6, 46.0, 41.2, 39.1, 38.6, 35.5, 31.3, 29.1, 20.7, 17.3, 7.1, 7.0, 5.3, 5.0;
FTIR, cm^{-1}: (thin film)	3327 (br), 2953 (s), 2876 (m), 1701 (s), 1456 (s), 1146 (s).

HRMS:	Calcd for $(C_{42}H_{63}ClN_2O_4Si_2+H)^+$	750.4015
(ESI)	Found	750.4088

TLC $R_f = 0.21$ (UV, *p*-anisaldehyde)

(2:1 hexane–ethyl acetate)

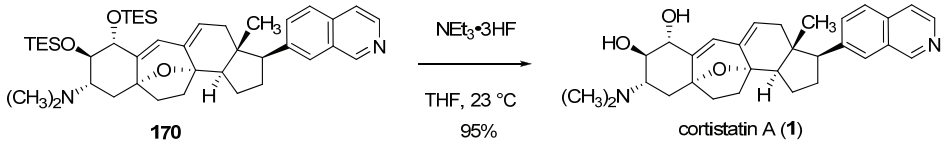


Cortistatin A Bis(triethylsilyl) Ether (**170**).

Trifluoroacetic anhydride (24.1 μL, 173 μmol, 5 equiv) was added dropwise to an ice-cooled solution of 1'-chloro-isoquinolyl alcohol **169** (26.0 mg, 35 μmol, 1 equiv), pyridine (28 μL, 346 μmol, 10 equiv) and 4-dimethylaminopyridine (2.1 mg, 17 μmol, 0.5 equiv) in dichloromethane (3.5 mL). After 30 min, the reaction mixture was partitioned between aqueous potassium phosphate buffer solution (pH 7.0, 0.2 M, 10 mL) and ethyl acetate (20 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (4:1 hexanes–ethyl acetate initially, grading to 2:1 hexanes–ethyl acetate) to provide the intermediate trifluoroacetate ester as a pale yellow foam.

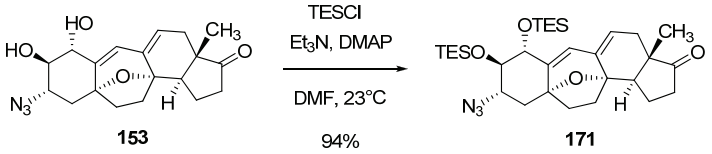
Benzene (0.6 mL + 2 × 0.2 mL wash) was added, and the resulting solution was transferred by cannula to a flame-dried, 10-mL Schlenk flask fitted with a stirring bar. The reaction flask was placed in a water bath at 23 ºC and volatiles were removed in vacuo through a 22-gauge needle in order to effect azeotropic drying. The flask was back filled with Ar and added a solution of 2,2'-azobisisobutyronitrile (17.2 mg, 105 μmol, 3.0 equiv) in benzene (0.7 mL). The reaction mixture was degassed by freeze-pump-thaw for four cycles. To the resulting solution was added tributyltin hydride (139 μL, 525 μmol,

15 equiv). The stopcock was closed and the reaction flask was placed in an oil bath preheated to 100 ºC. After 2 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. The product solution was directly purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate initially, grading to 4:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate) to afford cortistatin A bis(triethylsilyl) ether (**170**) as a pale yellow oil (17.1 mg, 70% over two steps). The spectral properties were identical to those previously reported.



Cortistatin A (**1**).

Triethylamine trihydrofluoride (39.5 μL, 242 μmol, 10 equiv) was added to a solution of cortistatin A bis(triethylsilyl) ether (**170**) (17.0 mg, 24.2 μmol, 1 equiv) in tetrahydrofuran (1.0 mL) at 23 ºC. After 30 min, the reaction mixture was partitioned between dichloromethane (20 mL) and a 1:1 mixture of saturated aqueous sodium chloride solution and saturated aqueous sodium bicarbonate solution (20 mL). The layers were separated. The aqueous layer was further extracted with dichloromethane (5 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (50:1 ethyl acetate–methanol initially, grading to 2:1 ethyl acetate–methanol, then 1:1 ethyl acetate–methanol) to afford cortistatin A (**1**) as a white solid (10.8 mg, 95%, >90% purity by ^{1}H NMR analysis). The spectral properties were identical to those previously reported.

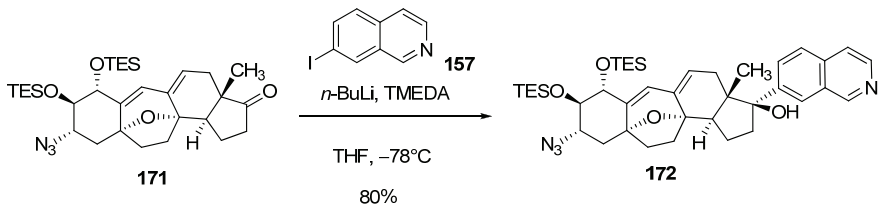


Azido Ketone **171** (Cortistatin A Primary Amine Series).

Chlorotriethylsilane (37 μL, 0.218 mmol, 6 equiv) was added dropwise to an ice-cooled solution of azido diol (**153**) (13.0 mg, 0.036 mmol, 1 equiv), triethylamine (51 μL, 0.364 mmol, 10 equiv), and 4-dimethylaminopyridine (8.9 mg, 0.073 mmol, 2 equiv) in *N,N*-dimethylformamide (1.0 mL). After 10 min, the ice bath was removed and the reaction flask was allowed to warm to 23 ºC. After 3 h, the reaction mixture was partitioned between ether (15 mL) and a 1:1:1 mixture of water, saturated aqueous sodium bicarbonate solution, and saturated aqueous sodium chloride solution (12 mL). The layers were separated. The aqueous layer was extracted with ether (4 × 10 mL). The organic layers were combined. The combined solution was washed with water (15 mL) and saturated aqueous sodium chloride solution (2 × 15 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate) to afford azido ketone **171** (cortistatin A primary amine series) as a pale yellow oil (20 mg, 94%).

^{1}H NMR: (500 MHz, $CDCl_3$) 6.08 (d, 1H, *J* = 1.8 Hz), 5.43 (dd, 1H, *J* = 4.5, 2.9 Hz), 3.97 (d, 1H, *J* = 8.7 Hz), 3.41 (t, 1H, *J* = 8.5 Hz), 3.33 (ddd, 1H, *J* = 12.1, 8.0, 4.3 Hz), 2.52 (dd, 1H, *J* = 19.2, 8.7 Hz), 2.38 (dd, 1H, *J* = 12.7, 5.8 Hz), 2.28–2.18 (m, 4H),

	2.18–2.09 (m, 3H), 1.97 (t, 1H, J = 12.6 Hz), 1.92–1.82 (m, 1H), 1.78–1.69 (m, 2H), 1.03–0.95 (m, 18H), 0.93 (s, 3H), 0.76–0.63 (m, 12H);
^{13}C NMR : (126 MHz, $CDCl_3$)	220.4, 141.8, 139.7, 120.5, 119.7, 81.3, 78.8, 78.5, 73.9, 62.6, 47.7, 47.2, 39.3, 37.4, 35.9, 33.9, 31.6, 18.9, 16.9, 7.0, 5.2, 5.0;
FTIR, cm^{-1}: (thin film)	2957 (s), 2878 (m), 2106 (vs), 1741 (vs), 1641 (m), 1460 (m), 1150 (s).
HRMS: (ESI)	Calcd for $(C_{31}H_{51}N_3O_4Si_2+Na)^+$ 608.3310 Found 608.3306
TLC (4:1 hexane–ethyl acetate)	R_f = 0.50 (UV, *p*-anisaldehyde)



Isoquinolyl Alcohol **172** (Cortistatin A Primary Amine Series).

A solution of *n*-butyllithium in hexanes (2.50 M, 68 μL, 0.171 mmol, 5 equiv) was added dropwise to a solution of 7-iodoisoquinoline (**157**) (43.5 mg, 0.171 mmol, 5 equiv) in tetrahydrofuran (2 mL) at –78 ºC, producing a dark red solution. After 30 min, *N,N,N',N'*-tetramethylethylenediamine (79 μL, 0.512 mmol, 15 equiv) was added. After 10 min, a solution of bistriethylsilyl ether ketone **171** (20 mg, 0.034 mmol, 1 equiv) in tetrahydrofuran (0.5 mL) was added via cannula. The flask containing **171** was rinsed with tetrahydrofuran (2 × 0.2 mL), and the rinses were added to the reaction mixture. After 30 min, saturated aqueous sodium bicarbonate solution (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (15 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate initially, grading to 4:1 hexanes–ethyl acetate, then 1:1 hexanes–ethyl acetate) to afford isoquinolyl alcohol **172** (cortistatin A primary amine series) as a pale yellow oil (12.2 mg, 50%), and,

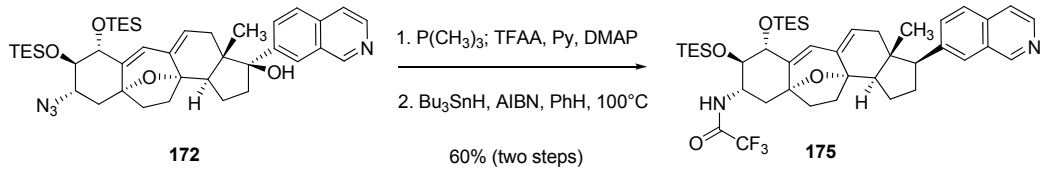
separately, recovered azido ketone **171** (cortistatin A primary amine series) (6.0 mg, 30%).

^{1}H NMR: (500 MHz, $CDCl_3$)	9.23 (s, 1H), 8.50 (d, 1H, *J* = 5.9 Hz), 7.93 (br s, 1H), 7.85 (dd, 1H, *J* = 7.3, 2.9 Hz), 7.76 (d, 1H, *J* = 8.8 Hz), 7.61 (d, 1H, *J* = 5.9 Hz), 5.96 (d, 1H, *J* = 1.5 Hz), 5.20 (dd, 1H, *J* = 4.9, 2.4 Hz), 3.92 (d, 1H, *J* = 7.8 Hz), 3.34–3.24 (m, 2H), 2.63 (ddd, 1H, *J* = 14.0, 9.6, 4.6 Hz), 2.45 (dd, 1H, *J* = 11.0, 9.0 Hz), 2.39 (app t, 1H, *J* = 11.2 Hz), 2.31 (app td, 1H, *J* = 13.6, 5.6 Hz), 2.20–2.04 (m, 4H), 1.95–1.87 (m, 2H), 1.77 (app dt, 1H, *J* = 12.7, 8.3 Hz), 1.69 (dd, 1H, *J* = 19.0, 10.3 Hz), 1.55 (d, 1H, *J* = 18.1 Hz), 1.21 (t, 1H, *J* = 7.1 Hz), 1.16 (s, 3H), 0.98–0.91 (m, 18H), 0.71–0.59 (m, 12H);
^{13}C NMR : (126 MHz, $CDCl_3$)	152.9, 145.2, 143.1, 141.2, 138.3, 134.8, 130.2, 128.0, 125.7, 125.2, 121.9, 119.9, 119.7, 85.6, 81.9, 78.7, 78.3, 73.8, 62.6, 47.5, 45.8, 39.2, 39.0, 37.9, 35.4, 31.3, 20.7, 17.2, 7.0, 7.0, 5.1, 5.0;
FTIR, cm^{-1}: (thin film)	3956 (br), 2955 (s), 2104 (s), 1641 (vs), 1390 (s), 1375 (s), 1250 (vs).

HRMS:	Calcd for $(C_{40}H_{58}N_4O_4Si_2+H)^+$	715.4069
(ESI)	Found	715.5050

TLC $R_f = 0.18$ (UV, *p*-anisaldehyde)

(2:1 hexane–ethyl acetate)



172 **175**

Trifluoroacetamide **175** (Cortistatin A Primary Amine Series).

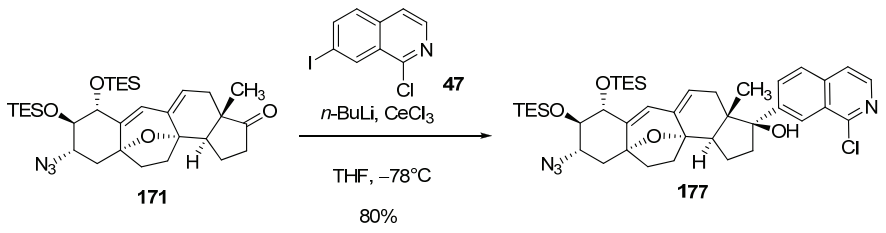
A solution of trimethylphosphine in toluene (1.0 M, 35 μL, 35 μmol, 5 equiv) was added to a solution of azido isoquinolyl alcohol **172** (cortistatin A primary amine series) (5.0 mg, 7.0 μmol, 1 equiv) in benzene (1.5 mL). The reaction flask was placed in an oil bath pre-heated to 55ºC. After 1.5 h, the reaction flask was cooled in an ice bath. Pyridine (11 μL, 140 μmol, 20 equiv) and 4-dimethylaminopyridine (0.85 mg, 7.0 μmol, 1 equiv) were added followed by trifluoroacetic anhydride (9.7 μL, 70 μmol, 10 equiv). After 30 min, the reaction mixture was partitioned between aqueous potassium phosphate buffer solution (pH 7.0, 0.2 M, 10 mL) and ethyl acetate (10 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate initially, grading to 4:1 hexanes–ethyl acetate) to provide the intermediate trifluoroacetate ester as a colorless oil.

Benzene (0.6 mL+ 2 × 0.2 mL wash) was added, and the resulting solution was transferred by cannula to a 10-mL microwave vessel (CEM Corporation, cat. #908035), to which a cap had been affixed by crimping. The vessel was placed in a water bath at 23 ºC and volatiles were removed in vacuo through a 22-gauge needle in order to effect

azeotropic drying. Benzene (0.65 mL) was added to the oily residue. To the resulting solution was added a solution of 2,2'-azobisisobutyronitrile (3.4 mg, 21 μmol, 3.0 equiv) in benzene (50 μL). The reaction mixture was degassed by sparging for 20 min with a slow stream of argon gas through a 22-gauge stainless steel needle. Tributyltin hydride (15 μL, 56 μmol, 8.0 equiv) was then added. The vessel cap was sealed with Teflon® tape and then Parafilm®. After sealing, the vessel was placed in an oil bath preheated to 100 ºC. After 1 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. The reaction mixture was directly purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate initially, grading to 4:1 hexanes–ethyl acetate) to furnish trifluoroacetamide **175** (cortistatin A primary amine series) as a pale yellow oil (3.2 mg, 60% over two steps).

^{1}H NMR: (500 MHz, $CDCl_3$) 9.23 (s, 1H), 8.50 (d, 1H, *J* = 5.9 Hz), 8.06 (d, 1H, *J* = 6.8 Hz), 7.80 (s, 1H), 7.77 (d, 1H, *J* = 8.3 Hz), 7.63 (d, 1H, *J* = 5.9 Hz), 7.59 (d, 1H, *J* = 8.3 Hz), 6.07 (s, 1H), 5.40 (d, 1H, *J* = 2.9 Hz), 4.15 (d, 1H, *J* = 5.9 Hz), 3.85 (br d, 1H, *J* = 3.4 Hz), 3.59 (d, 1H, *J* = 5.4 Hz), 3.18 (app t, 1H, *J* = 10.0 Hz), 2.42 (dd, 1H, *J* = 11.7, 8.3 Hz), 2.38–2.32 (m, 2H), 2.28–2.17 (m, 2H), 2.12 (t, 1H, *J* = 10.0 Hz), 2.02 (dd, 1H, *J* = 8.8, 4.4 Hz), 1.95 (dd, 1H, *J* = 17.6, 5.4 Hz), 1.87–1.79 (m, 2H), 1.75–1.67 (m, 1H), 1.32–1.24 (m, 2H), 1.02–0.93 (m, 18H), 0.75 (q, 6H, *J* = 7.8 Hz), 0.63 (q, 6H, *J* = 7.8 Hz), 0.56 (s, 3H);

^{13}C NMR :	156.2 (q, J = 35.7 Hz), 152.3, 142.5, 141.5, 140.0, 139.7,	
(126 MHz, $CDCl_3$)	134.7, 132.0, 128.1, 126.3, 125.9, 121.5, 120.2, 120.0,	
	84.3, 80.7, 79.9, 75.3, 56.8, 53.3, 51.9, 44.5, 40.0, 38.1,	
	30.6, 29.7, 29.3, 26.4, 20.6, 15.3, 7.0, 6.9, 4.8;	
^{19}F NMR :	−76.7 (s);	
(470 MHz, $CDCl_3$)		
FTIR, cm^{-1}:	3315 (br), 2955 (s), 2928 (vs), 1724 (vs), 1458 (m), 1379	
(thin film)	(m), 1279 (m).	
HRMS:	Calcd for $(C_{42}H_{59}F3N_2O_4Si_2+H)^+$	769.4038
(ESI)	Found	769.4054
TLC	R_f = 0.14 (UV, *p*-anisaldehyde)	
(4:1 hexane–ethyl acetate)		



1'-Chloro-Isoquinolyl Alcohol **177** (Cortistatin A Primary Amine Series).

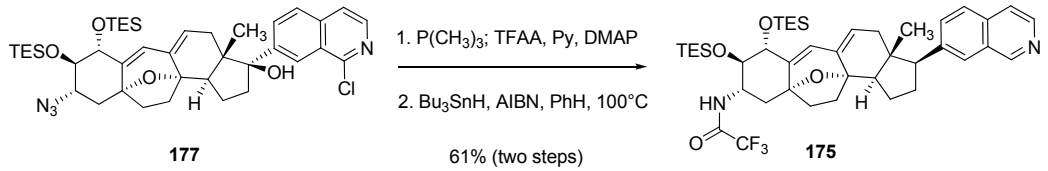
To a flame-dried, 10-mL Schlenk flask fitted with a stirring bar was added anhydrous cerium(III) chloride powder (56.8 mg, 230 μmol, 10 equiv) in glovebox. The reaction flask was placed under high vacuum (0.5 mmHg) and heated in an oil bath at 90 ºC with vigorous stirring. After 2 h, the oil bath was removed. The reaction flask was back filled with Ar and cooled in an ice bath. Tetrahydrofuran (1.0 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The white suspension was stirred vigorously. After 16 h, a solution of 1-chloro-7-iodoisoquinoline (**47**) (36.7 mg, 127 μmol, 5.5 equiv) in tetrahydrofuran (0.2 mL) was added. The reaction flask was cooled to –78 ºC in a dry ice-acetone bath. A solution of *n*-butyllithium in hexanes (1.60 M, 72 μl, 115 μmol, 5 equiv) was added, producing a chartreuse suspension. After 30 min, a solution of dimethylamino ketone **171** (cortistatin A primary amine series) (13.5 mg, 23 μmol, 1 equiv) in tetrahydrofuran (0.2 mL) was added. After 30 min, saturated aqueous ammonium chloride solution (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between half-saturated aqueous sodium bicarbonate solution (10 mL) and ethyl acetate (15 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (4 × 10 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was

filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate initially, grading to 5:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate) to afford 1'-chloro-isoquinolyl alcohol **177** (cortistatin A primary amine series) as a pale yellow oil (13.8 mg, 80%).

^{1}H NMR: (500 MHz, $CDCl_3$)	8.35 (br s, 1H), 8.26 (d, 1H, *J* = 6.0 Hz), 7.86 (d, 1H, *J* = 9.2 Hz), 7.78 (d, 1H, *J* = 8.7 Hz), 7.57 (d, 1H, *J* = 5.5 Hz), 5.96 (s, 1H), 5.20 (dd, 1H, *J* = 5.0, 2.7 Hz), 3.92 (d, 1H, *J* = 7.8 Hz), 3.33–3.27 (m, 2H), 2.64 (ddd, 1H, *J* = 14.1, 9.5, 4.3 Hz), 2.46–2.35 (m, 2H), 2.32 (td, 1H, *J* = 13.4, 6.8 Hz), 2.20–2.09 (m, 3H), 1.96–1.88 (m, 2H), 1.81–1.74 (m, 1H), 1.69 (dd, 1H, *J* = 18.8, 10.1 Hz), 1.51 (d, 1H, *J* = 17.4 Hz), 1.28–1.23 (m, 1H), 1.17 (s, 3H), 1.00–0.91 (m, 18H), 0.72–0.58 (m, 12H);
^{13}C NMR : (126 MHz, $CDCl_3$)	151.9, 146.7, 141.6, 141.3, 138.3, 136.7, 130.9, 126.3, 126.2, 124.0, 121.8, 120.2, 119.6, 85.6, 81.8, 78.7, 78.3, 73.8, 62.6, 47.5, 45.9, 39.2, 39.0, 37.8, 35.4, 31.3, 20.7, 17.3, 7.0, 7.0, 5.1, 5.0;
FTIR, cm^{-1}: (thin film)	3343 (br), 2955 (m), 2934 (m), 2104 (s), 1604 (s), 1454 (s).

HRMS:	Calcd for $(C_{40}H_{57}ClN_4O_4Si_2+H)^+$	749.3680
(ESI)	Found	749.3670

TLC	R_f = 0.45 (UV, *p*-anisaldehyde)
(2:1 hexane–ethyl acetate)	

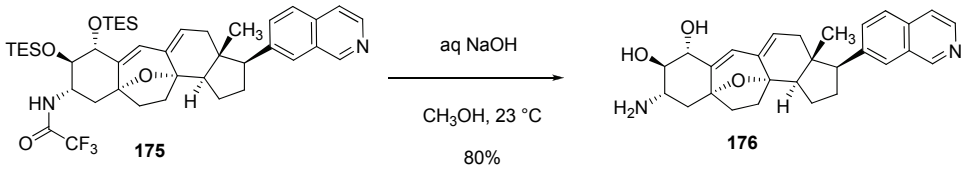


Trifluoroacetamide **175** (Cortistatin A Primary Amine Series).

A solution of trimethylphosphine in toluene (1.0 M, 77 μL, 77 μmol, 5 equiv) was added to a solution of 1'-chloro-isoquinolyl alcohol **177** (cortistatin A primary amine series) (11.5 mg, 15 μmol, 1 equiv) in benzene (3.0 mL). The reaction flask was placed in an oil bath pre-heated to 55ºC. After 1.5 h, the reaction flask was cooled in an ice bath. Pyridine (25 μL, 307 μmol, 20 equiv) and 4-dimethylaminopyridine (1.9 mg, 15 μmol, 1 equiv) were added followed by trifluoroacetic anhydride (21 μL, 153 μmol, 10 equiv). After 30 min, the reaction mixture was partitioned between aqueous potassium phosphate buffer solution (pH 7.0, 0.2 M, 15 mL) and ethyl acetate (15 mL). The layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 15 mL). The organic layers were combined. The combined solution was washed with saturated aqueous sodium chloride solution (10 mL) and the washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography on Davisil® silica gel (10:1 hexanes–ethyl acetate initially, grading to 4:1 hexanes–ethyl acetate) to provide the intermediate trifluoroacetate ester as a pale yellow solid.

Benzene (0.6 mL+ 2 × 0.2 mL wash) was added, and the resulting solution was transferred by cannula to a 10-mL microwave vessel (CEM Corporation, cat. #908035), to which a cap had been affixed by crimping. The vessel was placed in a water bath at 23 ºC and volatiles were removed in vacuo through a 22-gauge needle in order to effect

azeotropic drying. Benzene (0.70 mL) was added to the oily residue. To the resulting solution was added a solution of 2,2'-azobisisobutyronitrile (7.4 mg, 45 μmol, 3.0 equiv) in benzene (50 μL). The reaction mixture was degassed by sparging for 10 min with a slow stream of argon gas through a 22-gauge stainless steel needle. Tributyltin hydride (81 μL, 300 μmol, 20 equiv) was then added. The vessel cap was sealed with Teflon® tape and then Parafilm®. After sealing, the vessel was placed in an oil bath preheated to 100 ºC. After 1.5 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. The reaction mixture was directly purified by flash-column chromatography on Davisil® silica gel (40:1 hexanes–ethyl acetate initially, grading to 10:1 hexanes–ethyl acetate, then 4:1 hexanes–ethyl acetate) to furnish trifluoroacetamide **175** (cortistatin A primary amine series) as a pale yellow oil (7.0 mg, 61% over two steps). The spectral properties were identical to those previously reported.



Cortistatin A Primary Amine (**176**).

Aqueous sodium hydroxide solution (1.0 N, 0.20 mL) was added to a solution of trifluoroacetamide **175** (cortistatin A primary amine series) (2.1 mg, 2.7 μmol, 1 equiv) in methanol (0.80 mL) at 23 ºC. After 12 h, the reaction mixture was partitioned between a mixture of saturated aqueous sodium chloride solution (10 mL) and dichloromethane (10 mL). The layers were separated. The aqueous layer was further extracted with dichloromethane (5 × 10 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was directly used in subsequent steps without further purification (a pale yellow solid, 1.1 mg, 90%, >90% purity by ^{1}H NMR analysis).

^{1}H NMR: (500 MHz, $CDCl_3$) 9.22 (s, 1H), 8.49 (d, 1H, *J* = 5.9 Hz), 7.79 (s, 1H), 7.76 (d, 1H, *J* = 8.3 Hz), 7.63 (d, 1H, *J* = 5.4 Hz), 7.58 (d, 1H, *J* = 8.3 Hz), 6.19 (s, 1H), 5.43 (d, 1H, *J* = 2.9 Hz), 4.05 (d, 1H, *J* = 8.8 Hz), 3.20–3.09 (m, 2H), 2.72 (br ddd, 1H, *J* = 12.6, 9.6, 2.5 Hz), 2.51 (dd, 2H, *J* = 11.2, 8.8 Hz), 2.43–2.32 (m, 3H), 2.28 (app t, 2H, *J* = 11.2 Hz), 2.23–2.15 (m, 3H), 2.03 (dd, 2H, *J* = 12.7, 3.4 Hz), 1.97 (dd, 2H, *J* = 17.6, 5.4 Hz), 1.91–1.83 (m, 3H), 1.77 (app dt, 2H, *J* = 12.6, 8.1 Hz), 1.69 (dd, 2H, *J* = 17.6,

	9.3 Hz), 0.54 (s, 3H);	
FTIR, cm^{-1}: (thin film)	3350 (br), 2953 (s), 2928 (s), 2857 (m), 1699 (s), 1254 (s), 1038 (m).	
HRMS: (ESI)	Calcd for $(C_{28}H_{32}N_2O_3+H)^+$	445.2486
	Found	445.2482
TLC (methanol)	R_f = 0.14 (UV, *p*-anisaldehyde)	

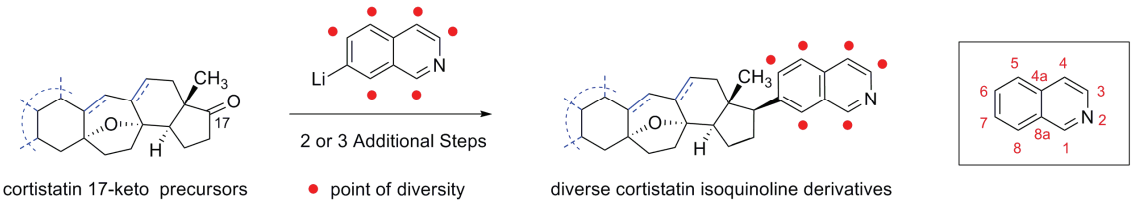
Chapter 4

A Versatile Synthesis of Substituted Isoquinolines

Introduction

The previous two chapters detailed an efficient and general approach towards the cortistatin family of natural products. In addition to natural cortistatins, our synthetic strategy should allow us to prepare a diverse array of cortistatin analogs. As described in Chapter 1, the isoquinoline substituent is known to be essential to the biological activity of the cortistatins. Therefore, we are particularly interested in preparing cortistatin analogs with differentially substituted isoquinolines, requiring a versatile methodology to synthesize differently substituted isoquinolines (Figure 4.1).

Figure 4.1 Diverse Cortistatin Derivatives by Isoquinoline Modification.



cortistatin 17-keto precursors

● point of diversity

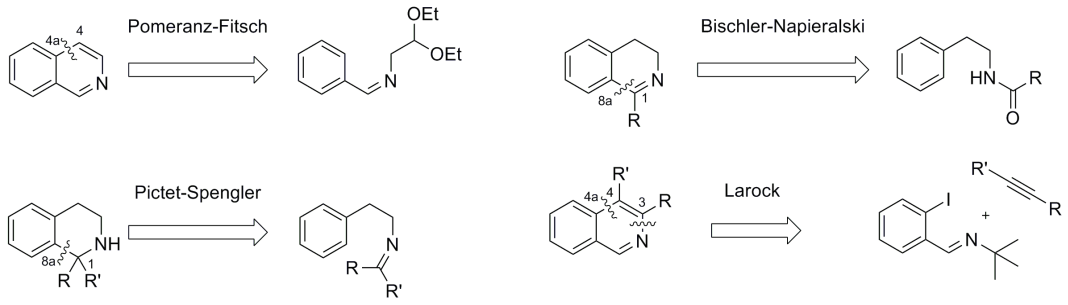
diverse cortistatin isoquinoline derivatives

Isoquinoline was first isolated by Hoogewerf and van Dorp from coal tar in 1885 and its structure was elucidated in the subsequent year.[1] Since then, isoquinolines have been recognized as one of the most important class of heterocycles: medicinally important isoquinolines include papaverine (used for multiple indications to improve blood flow),[2] fasudil (approved for the treatment of cerebral vasospasm in Japan),[3]

[1] Hoogewerff, S.; van Dorp, W. A., *J. Chem. Soc., Abstr*. **1886**, *50*, 478–479.
[2] Poch, G.; Kukovetz, W. R. *Life Science* **1971**, *10*, 133–144.
[3] (a) Asano, T.; Suzuki, T.; Tsuchiya, M.; Satoh, S.; Ikegaki, I.; Shibuya, M.; Suzuki, Y.; Hidaka, H.; *Br. J. Pharmacol* **1989**, *98*, 1091–1100. (b) Ono-Saito, N.; Niki, I.; Hidaka, H. *Phamacol. Ther.* **1999**, *82*, 123–131.

BMS-650032[4] and MK-1220[5] (candidates for the treatment of hepatitis C), and numerous dihydro-, tetrahydro-, as well as decahydro isoquinoline derivatives.[6]

Figure 4.2 Synthetic Approaches to Isoquinolines.



The literature approaches to construct this important class of heterocyclic rings are briefly summarized in Figure 4.2. Traditional methods to the synthesis of isoquinolines include the Pormeranz-Fitsch,[7] the Bischler-Napieralski,[8] and the Pictet-Spengler reactions;[9] however, their substrate scope is often limited due to the use of strong acids and elevated temperatures in the reaction condition. In recent years, Larock and co-workers have pioneered transition-metal-catalyzed annulation reactions to

[4] Pasquinelli, C.; Eley, T.; Villegas, C.; Sandy, K.; Mathias E.;, Wendelburg, P.; Liao, S.; McPhee, F.; Scola, P. M.; Sun, L. Q.; Marbury, T. C.; Lawitz, E.; Goldwater, R.; Rodriguez-Torres, M.; DeMicco, M. P.; Ababa, M.; Wright, D.; Charlton, M.; Kraft, W. K.; Lopez-Talavera, J. C.; Grasela, D. M. *Hepatology* **2009**, *50*, 411A.
[5] Rudd, M. T.; McCauley, J. A.; Butcher, J. W.; Romano, J. J.; McIntyre, C. J.; Nguyen, K. T.; Gilbert, K. F.; Bush, K. J.; Holloway, M. K.; Swestock, J.; Wan, B.; Carroll, S. S.; Dimuzio, J. M.; Graham, D. J.; Ludmerer, S. W.; Stahlhut, M. W.; Fandozzi, C. M.; Trainor, N.; Olsen, D. B.; Vacca, J. P.; Liverton, N. J. *ACS Med. Chem. Lett.* **2011**, *2*, 207–212.
[6] For a general review, see Bentley, K. W. In *The Isoquinoline Alkaloids*, CRC Press, **1998**.
[7] W. J. Gensler, In *Organic Reactions*, Vol. 6 (Eds: R. Adams), Wiley, New York, **1951**, pp. 191–206.
[8] W. M. Whaley, T. R. Govindachari, In *Organic Reactions*, Vol. 6 (Ed: R. Adams), Wiley, New York, **1951**, pp. 74–150.
[9] Whaley, W. M.; Govindachari. T. R. In *Organic Reactions*, Vol. 6 (Ed: R. Adams), Wiley, New York, **1951**, pp. 151-190.

construct isoquinoline rings from *o*-iodoaldimines and alkynes.[10,11] People have also used electrophilic cyclization reactions,[12] aryne annulation,[13] ring expansion,[14] and numerous other methods[15] to synthesize isoquinoline rings.

Despite the large number of known methods, however, literature routes to many of the isoquinoline structures we envisioned were either lengthy or impractical. Thus we decided to develop a new, versatile synthesis of substituted isoquinolines. Two important precedents informed our present work. The first was the Poindexter synthesis of 3-substituted isoquinoline (**191**) by deprotonation of *N*,2-dimethylbenzamide (**190**) and subsequent addition of the resulting *o*-tolylbenzamide dianions to nitriles followed by aqueous ammonium chloride workup (Scheme 4.1).[16] The second was the Forth method to prepare *o*-substituted benzaldehyde derivative (**193**) by metalation and subsequent alkylation of *o*-tolualdehyde *tert*-butylimines (**192**).[17,18] We imagined that trapping the

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[10] For early examples of using stoichiometric, transition-metal-mediated annulation reactions to construct isoquinolines, see: (a) Maassarani, F.; Pfeffer, M.; Le Borgne, G. *J. Chem. Soc., Chem. Commun.* **1987**, 565–567; (b) Wu, G.; Geib, S.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1988**, *53*, 3238–3241; (c) Girling, I. R.; Widdowson, D. A. *Tetrahedron Lett.* **1982**, *23*, 4281–4284.

[11] For selected examples of using transition-metal-catalyzed annulation reactions to construct isoquinolines, see: (a) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306–5307; (b) Roesch, K. R.; Zhang, H.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553–556; (c) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042–8051; (d) Dai, G.; Zhang, H.; Larock, R. C. *Org. Lett.* **2001**, *3*, 4035–4038; (e) Dai, G.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7042–7047; (f) Huang, Q.; Larock, R. C. *Tetrahedron Lett.* **2002**, 4*3*, 3557–3560; (g) Dai, G.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 920–928; (h) Huang, Q.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 980–988; (i) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 12050–12051; (j) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449–6457.

[12] For selected examples of using electrophilic cyclization reactions to construct isoquinolines, see: (a) Huang, Q.; Hunter, J. A.; Larock, R. C. *Org. Lett.* **2001**, *3*, 2973–2976; (b) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437–3444; (c) Fischer, D.; Tomeba, H.; Pahadi, N. K.; Patil, N. T.; Yomamoto, Y.; *Angew. Chem. Int. Ed.* **2007**, *46*, 4764–4766; (d) Fischer, D.; Tomeba, H.; Pahadi, N. K.; Patil, N. T.; Huo, Z.; Yomamoto, Y.; *J. Am. Chem. Soc.* **2008**, *130*, 15720–15725

[13] Gilmore, C. D.; Allan, K. M.; Stoltz, B, M. *J. Am. Chem. Soc.* **2008**, *130*, 1558–1559.

[14] Chiba, S.; Xu, Y.; Wang, Y. *J. Am. Chem. Soc.* **2009**, *131*, 12886–12887.

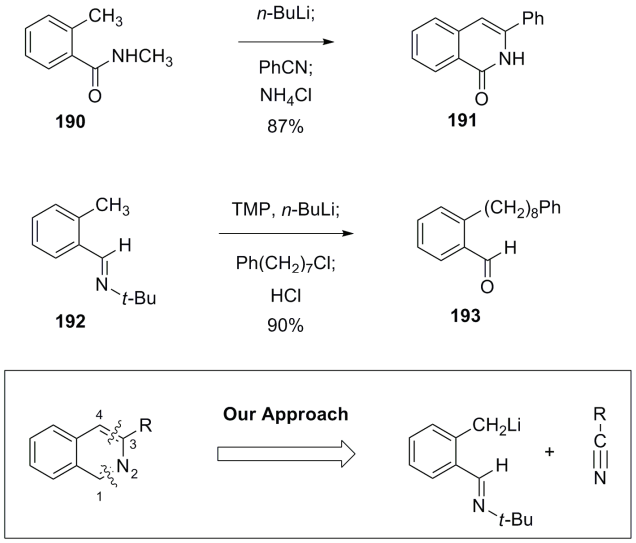
[15] For selected examples of other methods, see: (a)Wang, B.; Lu, B.; Jiang. Y.; Zhang, Y.; Ma, D. *Org. Lett.* **2008**, *10*, 2761–2763. (b) Sha, F.; Huang, X. *Angew. Chem. Int. Ed.* **2009**, *48*, 3458–3461; (c) Yang, Y.-Y.; Shou, W.-G.; Chen, Z.-B.; Hong, D.; Wang, Y.-G. *J. Org. Chem.* **2008**, *73*, 3928 – 3930.

[16] Poindexter, G.. S. *J. Org. Chem.* **1982**, *47*, 3787–3788.

[17] Forth, M. A.; Mitchell, M. B.; Smith, S. A. C.; Gombatz, K.; Snyder, L. *J. Org. Chem.* **1994**, *59*, 2616–2619.

metalated *o*-tolualdehyde *tert*-butylimine anions with nitriles might provide a direct route to 3-substituted isoquinolines. As detailed in this chapter, the chemistry proved to be much more versatile than we initially imagined, by virtue of transformations that ensue subsequent to addition of the nitrile.[19]

Scheme 4.1 Literature Precedents and Our Approach to Construct Isoquinoline Rings.



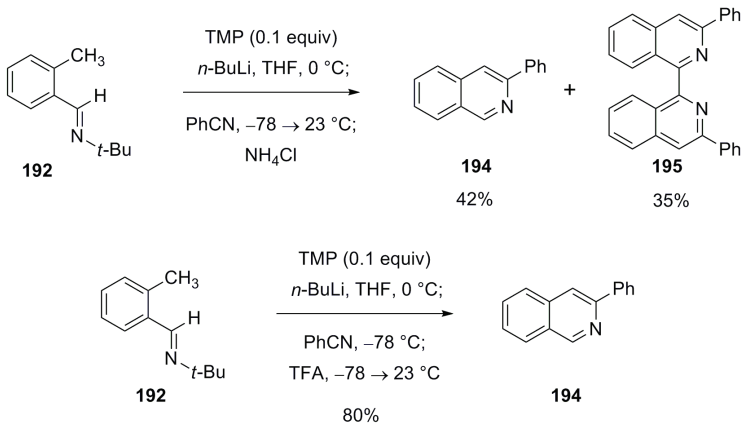
A Versatile Synthesis of Substituted Isoquinolines

Initial experiments were conducted in a simple system with the readily available *o*-tolualdehyde *tert*-butylimine (**192**, Scheme 4.2). The Forth's condition[17] was applied, in which *n*-butyllithium (1.05 equiv) was added slowly to an ice-cooled solution of *o*-

[18] *N*-Cyclohexyl aldimines have also been used to direct ortho-metalation: (a) Ziegler, F. E.; Fowler, K. W. *J. Org. Chem.* **1976**, *41*, 1564–1566; (b) Flippin, L. A.; Muchowski, J. M.; Carter, D. S. *J. Org. Chem.* **1993**, *58*, 2463–2467; (c) Forth, M. A.; Mitchell, M. B.; Smith, S. A. C.; Gombatz, K.; Snyder, L. *J. Org. Chem.* **1994**, *59*, 2616–2619.
[19] Si, C.; Myers, A. G. *Angew. Chem. Int. Ed.* **2011**, *50*, 10409–10413.

tolualdehyde *tert*-butylimine (**192**, 1 equiv) in the presence of a catalytic amount of tetramethylpiperidine (TMP, 0.10 equiv) in tetrahydrofuran (0.5 M) over 40 min, generating the *o*-tolyl anion as a deep purple solution. This deep purple solution was then cannulated to benzonitrile (1.5 equiv) at –78 ºC, forming a dark red solution within 3 min. Upon warming to 23 °C, the reaction mixture became dark brown. Aqueous work-up with ammonium chloride followed by chromatography purification provided 3-phenylisoquinoline (**194**) in 42% yield and, separately, 3,3'-diphenyl-1,1'-biisoquinoline (**195**), in 35% yield. This by-product probably arose by base-induced dimerization of 3-phenylisoquinoline followed by oxidation,[20] suggesting that formation of the isoquinoline ring had occurred prior to quenching with ammonium chloride. By adopting a different quenching protocol, addition of excess trifluoroacetic acid at –78 °C then warming to 23 °C, formation of **195** was avoided and 3-phenylisoquinoline (**194**) could be isolated in 80% yield.

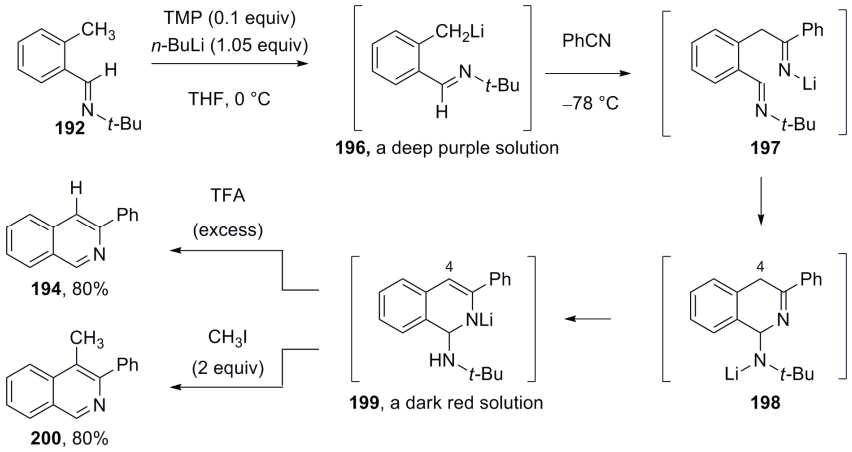
Scheme 4.2 Initial Studies to Synthesize 3-Substituted Isoquinoline.



[20] Clarke, J. E.; McNamara, S.; Meth-Cohn, O. *Tetrahedron Lett.* **1974**, *27*, 2373–2376.

Mechanistically, we considered that after the initial metalation, the deep purple anion **196** would add to benzonitrile, affording an imido anion **197**, which subsequently cyclized to give a *tert*-butylamido anion **198**. However, neither **197** nor **198** seemed likely to account for the dark red color that we observed upon addition of anion **196** to benzonitrile. We speculated that the *tert*-butylamido anion **198** might react further by intra- or intermolecular proton transfer to form an extended eneamido anion **199**, and this did appear to be a reasonable candidate to account for the red color we observed.[21] To test this hypothesis, methyl iodide (2 equiv) was added to the deep red solution shortly after its formation at –78 °C, producing an orange solution within minutes. Addition of trifluoroacetic acid (excess) after 30 min, also at –78 °C, followed by warming, aqueous workup, and chromatography purification provided 4-methyl-3-phenyl-isoquinoline (**200**) in 80% yield.[22,23]

Scheme 4.3 Synthesis of 4-Methyl-3-phenylisoquinoline (**200**) and a Plausible Mechanism.



[21] An alternative sequencing of steps is feasible; e.g., tautomerization of intermediate **197** may occur prior to ring closure to form **199**.

[22] Addition of alkyllithium reagents to C1 of isoquinolines is known to produce an adduct that can be trapped at C4, see: (a) Alexakis, A.; Amiot, F. *Tetrahedron: Asymmetry* **2002**, *13*, 2117–2122. b) Louërat, F. ; Fort, Y. ; Mamane, V. *Tetrahedron Lett.* **2009**, *50*, 5716–5718.

[23] 3,4-dihydro-l(2*H*)-isoquinolones have been synthesized by the condensation of *N,N*-diethyl-*o*-toluamide anions with aldimines. Lithiation (and subsequent trapping) of the benzylic position was reported in this study: Clark, R. D.; Jahangir *J. Org. Chem.* **1987**, *52*, 5378–5382.

As illustrated in Table 4.1, a wide range of substituted isoquinolines could be synthesized by the direct condensation of *o*-tolualdehyde *tert*-butylimine anions with different nitriles followed by electrophilic trapping at C4. The Forth protocol[17] was found to be quite general for the metalation of different *o*-tolualdehyde *tert*-butylimines, except for the halogenated ones, in which lithium diisopropylamide (LDA, 1.05 equiv) was found to be superior and led to higher yields (entries 2, 6 and 8). Entries 1–4 demonstrated the use of aliphatic nitriles as substrates and showed that a variety of alkyl halides were suitable for C4 alkylation, including ethyl iodide (entry 1), *n*-butyl iodide (entry 2), allyl bromide (entry 3), and benzyl bromide (entry 4). Although a number of potentially enolizable aliphatic nitriles were successfully employed, thus far, acetonitrile has not proven to be a viable coupling partner, likely because enolization was more rapid than addition to the nitrile.[24] Entries 5–9 illustrated that *N,N*-dialkylcyanamides were also effective substrates for the condensation, and the subsequent C4 trapping could be successfully achieved not only with alkylation reagents like *para*-bromobenzyl bromide (entry 5) and methyl iodide (to afford a hindered 4,5-dimethylisoquinoline structure, entry 7), but also with Mander's reagent to introduce a C4 carbomethoxy group (entry 6),[25] and with *N*-fluorobenzenesulfonimide to produce isoquinolines with C4 fluorine (entries 8 and 9). Entries 10–13 exemplified couplings with arylnitriles and trapping reactions for the introduction of C4 heteroatoms other than fluorine, including chlorine (using hexachloroethane, entry 10), oxygen [using oxodiperoxymolybdenum (pyridine)(hexamethylphosphoric triamide), MoOPH, entry 11],[26] sulfur (using methyl

[24] Poindexter had also noted that acetonitrile was not a suitable substrate in his method for isoquinolone formation, see: Ref 16.
[25] S. R. Crabtree, W. L. Alex Chu, L. N. Mander, *Synlett* **1990**, 169–170.
[26] Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188–196.

Table 4.1 Synthesis of a Wide Range of Substituted Isoquinolines by Condensation of Lithiated *o*-Tolualdehyde *tert*-Butylimines with Nitriles Followed by Trapping at C4 with Various Electrophiles.[a]

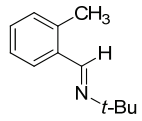
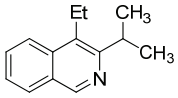
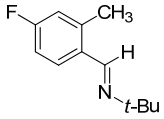
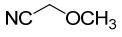
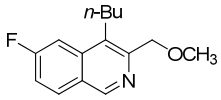
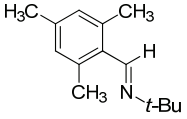
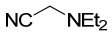
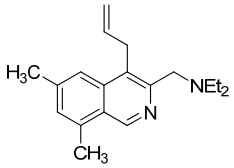
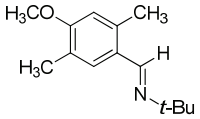
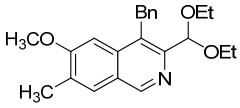
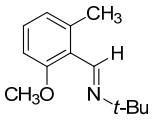
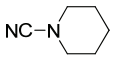
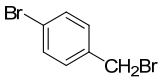
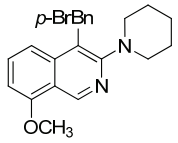
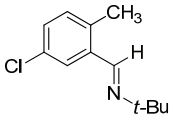
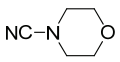
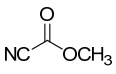
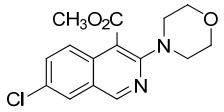
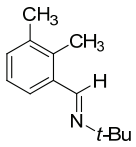
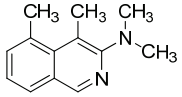
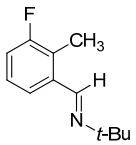
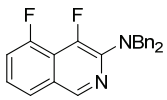
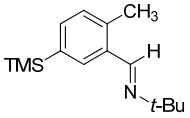
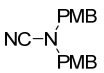
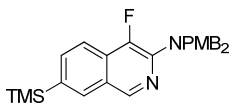
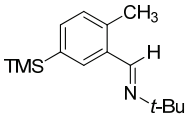
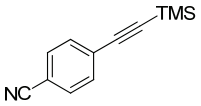
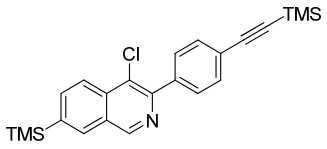
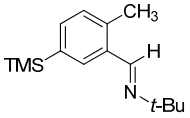
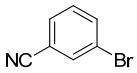
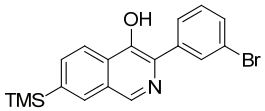
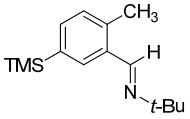
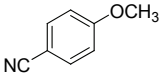
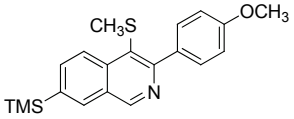
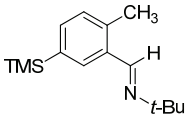
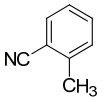
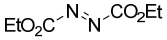
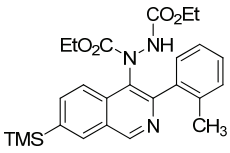
Entry	Imine	Nitrile	Electrophile	Product	Yield[b]
1			EtI		52
2[c]			*n*-BuI		50
3[d]					60
4			BnBr		50
5[d]					52
6[c]					66
7[d]			CH_3I		54
8[c]			NFSI		74
9			NFSI		60

Table 4.1 *(Continued)*

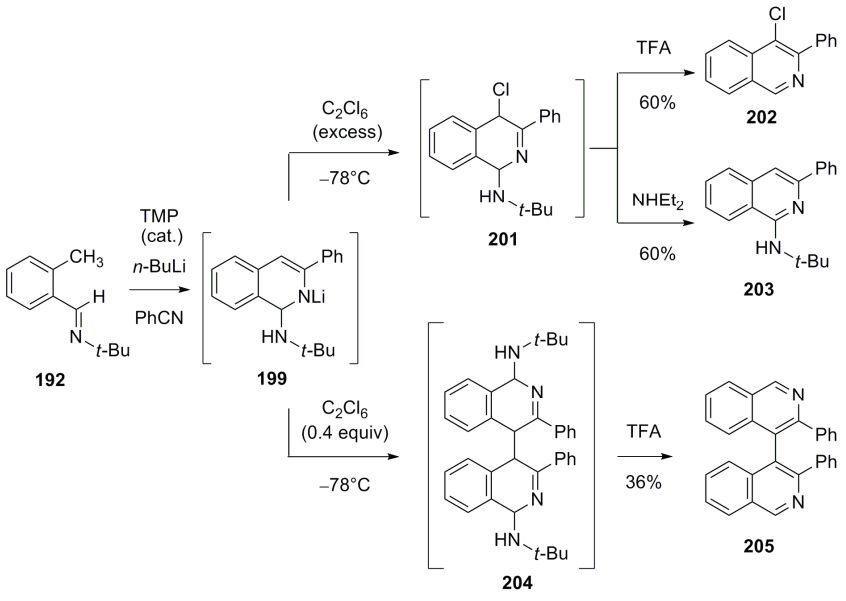
10[e]			C_2Cl_6		54
11[f]			MoOPH		40
12[d]			CH_3SSCH_3		68
13[d]					55

[a] For transformations with enolizable nitriles as substrates (entries 1–4) the nitriles were used as the limiting reagent (1 equiv) and the *tert*-butylaldimines were used in excess (1.25 equiv); in most other cases the *tert*-butylaldimine was used as the limiting reagent (1 equiv) and the nitrile was used in excess (1.25–1.5 equiv). Metalation of the *tert*-butylaldimine was achieved by the method of Forth *et al.*[17] [b] Isolated yields based on the limiting reagent. In the fluorinations of entries 8 and 9 the fluorinating agent *N*-fluorobenzene-sulfonimide (NFSI) was used as the limiting reagent (the *tert*-butylaldimine was used in excess, 1.25 equiv). [c] With the halogenated *tert*-butylaldimine substrates of entries 2, 6, and 8, lithium diisopropylamide (LDA, 1.05 equiv) was used for metalation in lieu of TMP-*n*-BuLi. [d] Hexamethylphosphoramide (HMPA, 2 equiv) was added prior to the addition of the electrophile. [e] Electrophilic trapping with hexachloroethane was conducted by addition of the reaction mixture by cannula to a large excess of the electrophile (4 equiv) at –78 °C. [f] Potassium hexamethyldisilazide (KHMDS, 1 equiv) was added just prior to addition of MoOPH (1.5 equiv).

disulfide, entry 12), and nitrogen (using diethylazodicarboxylate, entry 13). In the latter two instances we found that the efficiencies of C4 trapping were enhanced in the presence of the additive hexamethylphosphoramide (HMPA, 2 equiv). This additive also proved to enhance the yield of C4-alkylation products in the cases of entries 3, 5, and 7, which we believe was due to acceleration of an otherwise slow proton-transfer reaction that formed the eneamido anion intermediate.[27]

4-Chloroisoquinolines, 1-*tert*-butylamino isoquinolines, or 4,4'-biisoquinolines were obtained selectively by modification of the protocol after trapping with hexachloroethane (Scheme 4.4). After metalation and condensation with benzonitrile, the putative eneamido anion **199** was quenched by addition to an excess of hexachloroethane (4 equiv) at –78 °C. Work-up under standard acidic conditions, with excess

Scheme 4.4 Selective Preparation of Isoquinolines by Variation of Reaction Conditions.

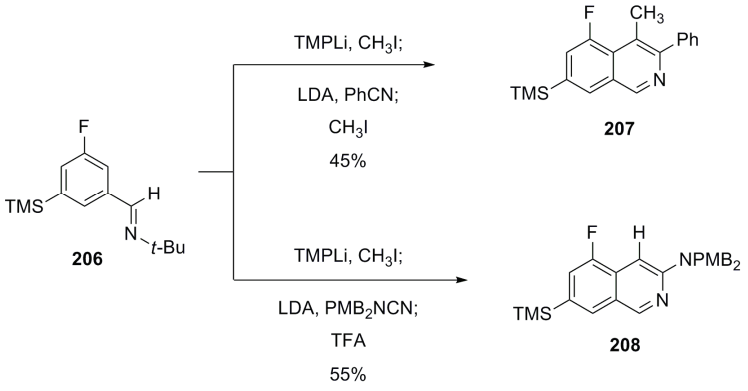


[27] In the absence of HMPA C4-unsubstituted isoquinolines were formed as major by-products in each of these cases; In the cases of entries 3, 5, and 7, where proton transfer to form the eneamide intermediate is believed to be slow, addition of HMPA caused a noticeable darkening of the red or orange solutions.

trifluoroacetic acid, led to the expected 4-chloroisoquinoline product **202** (also see Table 4.1, entry 10). Interestingly, using an alternative basic work-up procedure with excess diethylamine, elimination of hydrogen chloride in intermediate **201** occurred, providing 1-*tert*-butylamino isoquinoline derivative **203**, which proved valuable for subsequent diversification of C1. Also, upon addition of substoichiometric amount of the electrophile (0.4 equiv, added slowly) to the eneamido anion **199**, a 4,4'-biisoquinoline derivative **205** was formed as the primary product,[28] which likely arose from the dimerization product **204** formed between the remaining 4-lithiated isoquinolinyl intermediate **199** and the newly formed 4-choloro isoquinolinyl intermediate **201**.

With *tert*-butylaldimine substrates containing a second ortho directing group, such as a 3-fluoro substituent, it was possible to assemble substituted isoquinolines from as many as four components in sequence in a single operation (Scheme 4.5). For example, metalation of 3-fluoro-5-(trimethylsilyl)benzaldehyde *tert*-butylimine (**206**) with lithium

Scheme 4.5 One-pot Synthesis of Isoquinolines from Aldimines with a Second *o*-Directing Group.



[28] For an example where an isoquinolinyl dimer was formed by a similar mechanism, see: Ref 22b.

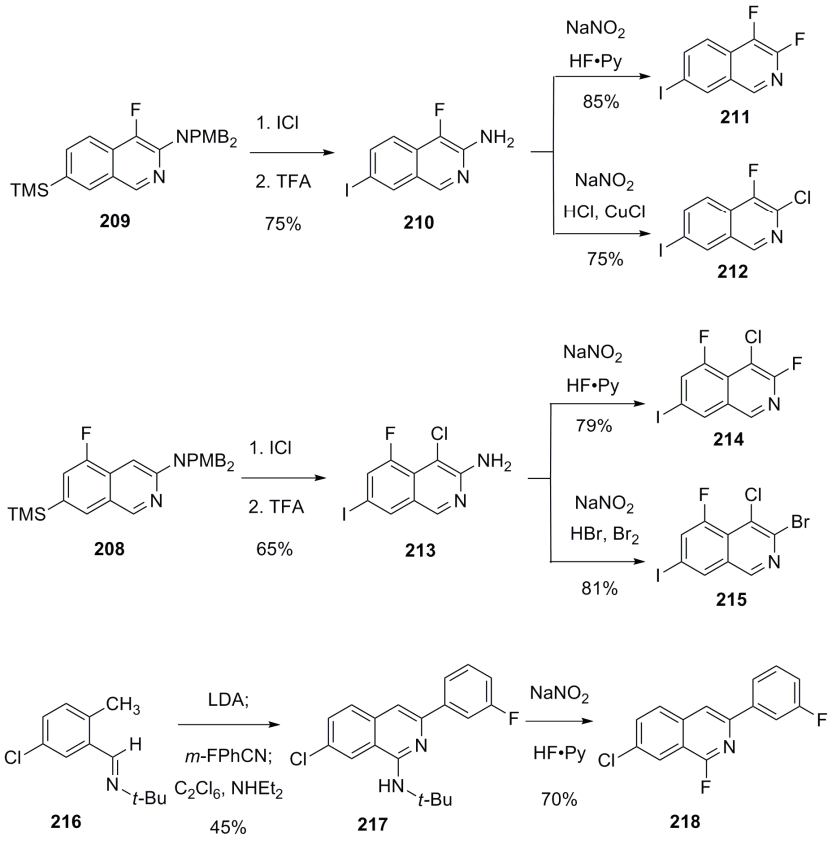
2,2,6,6-tetramethylpiperidide (LTMP, 1.05 equiv) initially formed an *o*-lithio intermediate that was trapped with methyl iodide (0.90 equiv); subsequent deprotonation of the methylated product in the same pot with lithium diisopropylamide (LDA, 1.05 equiv) at –40 ºC formed a dark red solution of the presumed *o*-tolyl anion; addition of benzonitrile, followed by C4-trapping with a second equivalent of methyl iodide afforded 5-fluoro-4-methyl-3-phenyl-7-(trimethylsilyl)isoquinoline (**207**) in 45% yield. A second example featured a simpler, three-component assembly by condensation of the presumed *o*-tolyl anion with *N,N*-bis(p-methoxybenzyl)cyanamide to provide isoquinoline **208** in 55% yield, which proved to be a highly versatile intermediate for further elaboration (see below).

Some of the isoquinolines prepared above could be further derivatized to highly halogenated structures (Scheme 4.6). For example, treatment isoquinoline **209** (prepared in Table 4.1, entry 9) with iodine monochloride in dichloromethane at 0 °C afforded product of 7-iododesilylation;[29] subsequent addition of trifluoroacetic acid (neat) led to cleavage of the *p*-methoxybenzyl groups, providing 3-amino-4-fluoro-7-iodoisoquinoline (**210**) in 75% yield. Diazotization of the latter product **210** in the presence of fluoride and chloride sources gave rise to the corresponding 3-fluoroisoquinoline **211** and 3-chloroisoquinoline **212** in good yields. Application of the same sequence to isoquinoline **208** (prepared in Scheme 4.5) proceeded with chlorination at C4 followed by a slower 7-iododesilylation reaction during initial treatment with iodine monochloride;[30] subsequent deprotection provided a 3-aminoisoquinoline **213**, which was further transformed to polyhalogenated isoquinolines **214** and **215**. Lastly, 1-*tert*-butylaminoisoquinoline

[29] Stock, L. M.; Spector, A. R. *J. Org. Chem.* **1963**, *28*, 3272–3274.
[30] Iodine monochloride chlorinates in polycyclic aromatic compounds, see: Turner, D. E.; O'Malley, R. F.; Sardella, D. J.; Barinelli, L. S.; Kaul, P. *J. Org. Chem.* **1994**, *59*, 7335–7340.

derivatives **217**, prepared by a modified basic work-up (see Scheme 4.4), was transformed directly into 1-fluoroisoquinoline **218** by dealkylative diazotization in the presence of fluoride ions,[31] which we anticipate should allow for further diversification of position C1 by standard nucleophilic aromatic substitution reactions. These isoquinolines with a halogen-handle at C7 should find applications in the synthesis of cortistatin analogs, which is the currently ongoing in our laboratory.

Scheme 4.6 Preparation of Poly-halogenated Isoquinolines.

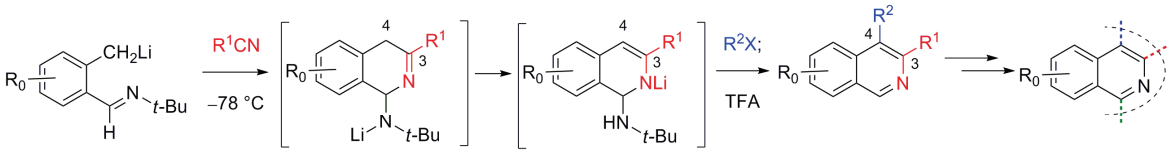


[31] In contrast, the transformation of isoquinolones to 1-fluoroisoquinolines can be low yielding, see: Zhu, G.-D.; Gong, J.; Claiborne, A.; Woods, K. W.; Gandhi, V. B.; Thomas, S.; Luo, Y.; Liu, X.; Shi, Y.; Guan, R.; Magnone, S. R.; Klinghofer, V.; Johnson, E. F.; Bouska, J.; Shoemaker, A.; Oleksijew, A.; Stoll, V. S.; Jong, R. D.; Oltersdorf, T.; Li, Q.; Rosenberg, S. H.; Giranda, V. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3150–3155.

Conclusion

In summary, we have developed a versatile synthesis of substituted isoquinolines, in which lithiated *o*-tolualdehyde *tert*-butylimines were condensed with a wide range of nitriles to form eneamido anion intermediates that were trapped *in situ* with various electrophiles, affording a diverse array of highly substituted isoquinolines, many of which were difficult to access by known methods (Figure 4.4). Further substitutional diversification can be achieved by modification of the work-up conditions and by subsequent transformations. This method should be useful for the preparation of many biological active isoquinolines, especially for the synthesis of cortistatin analogs with isoquinoline modifications.

Figure 4.4 Summary of Our Synthetic Approach to Substituted Isoquinolines.



R_1 = alkyl, aryl, NR_2;
R_2 = alkyl, allyl, benzyl, F, Cl, O, S, N.

Experimental Section

General Experimental Procedures. All reactions were performed in round-bottom flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation (house vacuum, ca. 25–40 Torr) at ambient temperature, unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60 Å pore-size, 230–400 mesh, Merck KGA) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light, then were stained with either an aqueous sulfuric acid solution of ceric ammonium molybdate (CAM) or acidic ethanolic *p*-anisaldehyde solution (*p*-anisaldehyde) followed by brief heating on a hot plate. Flash-column chromatography was performed as described by Still *et al.*,[32] employing silica gel (60 Å, 32–63 μM, standard grade, Dynamic Adsorbents, Inc.).

Materials. Commercial solvents and reagents were used as received with the following exceptions. 2,2,6,6-Tetramethylpiperidine, diisopropylamine, benzonitrile, isobutyronitrile, diethylamine, trimethylsilyl chloride, and hexamethylphosphoramide were distilled from calcium hydride under an atmosphere of argon or dinitrogen. Tetrahydrofuran was purified by the method of Pangborn *et al*.[33] *N*-fluorobenzenesulfonimide was recrystallized from ether. Iodomethane, iodoethane, 1-iodobutane, allyl bromide, benzyl bromide, and dimethyl disulfide were passed through

[32] W. C. Still, M. Khan, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.
[33] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518–1520.

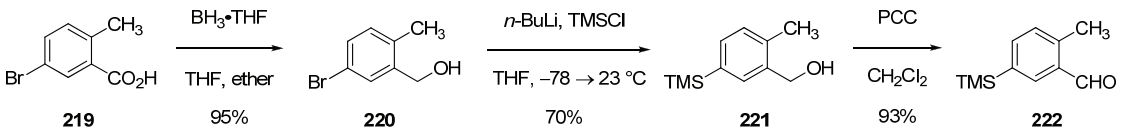
basic alumina immediately prior to use. 2-Methoxyl-6-methylbenzaldehyde [34] and oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) (MoOPH) [35] were prepared according to literature procedures. The molarity of *n*-butyllithium solutions was determined by titration against a standard solution of diphenylacetic acid in tetrahydrofuran (average of three determinations).[36]

Instrumentation. Proton magnetic resonance (^{1}H NMR) spectra were recorded on Varian INOVA 400 (400 MHz), 500 (500 MHz) or 600 (600 MHz) NMR spectrometers at 23 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to residual protium in the NMR solvent ($CHCl_3$, δ 7.26). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br = broad, app = apparent), integration, and coupling constant (*J*) in Hertz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on Varian INOVA 500 (126 MHz) NMR spectrometers at 23 °C. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, δ 77.0; C_6D_6, δ 128.0). Fluorine nuclear magnetic resonance spectra (^{19}F NMR) were recorded on Varian INOVA 500 (470 MHz) NMR spectrometers at 23 °C. Infrared (IR) spectra were obtained using a Shimadzu 8400S FT-IR spectrometer and were referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (vs = very strong, s = strong, m = medium, w = weak, br = broad). High-resolution mass spectra were obtained at the Harvard University Mass Spectrometry

[34] F. M. Hauser,S. R. Ellenberger, *Synthesis* **1987**, 723–724.
[35] E. Vedejs, D. A. Engler, J. E. Telschow, *J. Org. Chem.* **1978**, *43*, 188–196.
[36] W. G. Kofron, L. M. Baclawski, *J. Org. Chem.* **1976**, *41*, 1879–1880.

Facility. Melting points were measured using a Thomas Hoover uni-melt apparatus (6427F10) and were uncorrected.

*(For clarity, intermediates that have not been assigned numbers in the text are numbered sequentially in the Supporting Information beginning with **219**.)*



2-Methyl-5-(trimethylsilyl)benzaldehyde (**222**)

A solution of borane-tetrahydrofuran in tetrahydrofuran (1.0 M, 123 mL, 123 mmol, 1.2 equiv) was added dropwise to a solution of 5-bromo-2-methylbenzoic acid (**219**, 22.0 g, 102 mmol, 1 equiv) in ether (120 mL) (CAUTION: gas evolution). After 1 h, the reaction flask was placed in an oil bath preheated to 50 ºC. After 2 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. Methanol (20 mL) was added dropwise (gas evolution) and the product solution was concentrated to remove the bulk of solvent. The residue was purified by flash-column chromatography (10:1 initially, grading to 5:1 hexanes–ethyl acetate) to provide **220** as a white solid (19.5 g, 95%).

A solution of *n*-butyllithium in hexanes (2.50 M, 77.6 mL, 194 mmol, 2.0 equiv) was added dropwise to a cooled solution of **220**, (19.5 g, 97 mmol, 1 equiv) in tetrahydrofuran (200 mL) at –78 ºC. After 40 min, chlorotrimethylsilane (25.8 mL, 204 mmol, 2.1 equiv) was added. After 30 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 30 min, aqueous hydrochloric acid solution (4.0 N, 50 mL) was added. The product solution was concentrated to remove the bulk of solvent. The concentrate was partitioned between water (100 mL) and 2:1 hexanes–ethyl acetate (300 mL). The layers were separated. The aqueous layer was extracted with 2:1 hexanes–ethyl acetate (2 × 100 mL). The organic layers were combined. The combined solution was washed sequentially with water (100 mL), saturated aqueous sodium bicarbonate solution (100 mL), and saturated aqueous sodium chloride solution (100 mL). The washed solution was dried over sodium sulfate. The

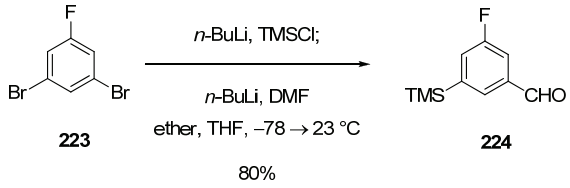
dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (40:1 initially, grading to 20:1 then 10:1 hexanes–ethyl acetate), furnishing **221** as a colorless oil (13.2 g, 70%).

Pyridinium chlorochromate (22.0 g, 102 mmol, 1.5 equiv) was added to an ice-cooled solution of **221**, (13.2 g, 67.9 mmol, 1 equiv) in dichloromethane (120 mL). After 30 min, the cooling bath was removed. After 1 h, the reaction mixture was filtered through silica, washing with dichloromethane (3 × 100 mL). The filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate) to furnish 2-methyl-5-(trimethylsilyl)benzaldehyde (**222**) as a colorless oil (12.1 g, 93%).

^{1}H NMR: (400 MHz, $CDCl_3$)	10.30 (s, 1H), 7.93 (d, 1H, J = 1.5 Hz), 7.62 (dd, 1H, J = 7.3, 1.5 Hz), 7.25 (d, 1H, J = 7.3 Hz), 2.67 (s, 3H), 0.30 (s, 9H).
^{13}C NMR : (100 MHz, $CDCl_3$)	193.3, 141.1, 138.5, 138.4, 137.2, 133.4, 131.2, 19.6, –1.2.
FTIR, cm^{-1}: (thin film)	2957 (m), 1697 (vs), 1595 (m), 1265 (m), 1250 (s).

HRMS:	Calcd for $(C_{11}H_{16}OSi+H)^+$	193.1043
(ESI)	Found	193.1051

TLC (9:1 hexanes–ethyl acetate)	R_f = 0.49 (UV)



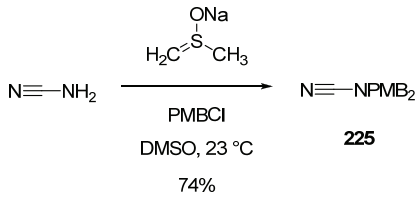
3-Fluoro-5-(trimethylsilyl)benzaldehyde (**224**)[37]

1,3-Dibromo-5-fluorobenzene (**223**, 2.52 mL, 20 mmol, 1 equiv) was added dropwise to a cooled solution of *n*-butyllithium (2.50 M in hexanes, 8.0 mL, 20 mmol, 1 equiv) in ether (40 mL) at –78 ºC. After 40 min, chlorotrimethylsilane (2.54 mL, 20 mmol, 1 equiv) was added, followed by the addition of tetrahydrofuran (40 mL). After 40 min, a second portion of *n*-butyllithium (2.50 M in hexanes, 8.8 mL, 22 mmol, 1.1 equiv) was added. After 30 min, *N,N*-dimethylformamide (4.65 mL, 60 mmol, 3 equiv) was added. After 40 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 1 h, the product solution was concentrated to remove the bulk of solvent. The concentrate was partitioned between 2:1 hexanes–ethyl acetate (150 mL) and saturated aqueous sodium bicarbonate solution (50 mL). The layers were separated. The organic layer was washed with saturated aqueous sodium chloride solution (50 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (100:1 hexanes–ethyl acetate initially, grading to 40:1 hexanes–ethyl acetate, then 20:1 hexanes–ethyl acetate), furnishing 3-fluoro-5-(trimethylsilyl)benzaldehyde (**224**) as a yellow oil (3.14 g, 80%).

^{1}H NMR: 10.02 (dd, 1H, J = 1.8, 0.9 Hz), 7.78 (s, 1H), 7.51 (ddd,

[37] P. Kurach, S. Luliński, J. Serwatowski, *Eur. J. Org. Chem.* **2008**, 3171–3178.

(500 MHz, $CDCl_3$)	1H, J = 8.6, 2.6, 1.6 Hz), 7.45 (ddd, 1H, J = 8.2, 2.3, 1.4 Hz), 0.32 (d, 10H, J = 0.9 Hz).	
^{19}F NMR :	–113.1 (ddd, J = 8.2, 8.0, 2.3 Hz).	
(470 MHz, $CDCl_3$)		
^{13}C NMR :	191.4 (d, J = 1.8 Hz), 162.9 (d, J = 251.7 Hz), 145.4 (d,	
(126 MHz, $CDCl_3$)	J = 3.7 Hz), 137.8 (d, J = 5.5 Hz), 130.7 (d, J = 2.7 Hz), 125.9 (d, J = 19.2 Hz), 115.5 (d, J = 21.1 Hz), –1.4.	
FTIR, cm^{-1}:	2957 (m), 1703 (vs), 1582 (m), 1375 (s), 1254 (vs).	
(thin film)		
HRMS:	Calcd for $(C_{10}H_{13}FOSi+H)^+$	197.0798
(ESI)	Found	197.0790
TLC	R_f = 0.49 (UV)	
(9:1 hexanes–ethyl acetate)		



N,N-bis(4-methoxybenzyl)cyanamide (**225**)[38]

Cyanamide (2.10 g, 50 mmol, 1 equiv) was added portionwise over 10 min to a suspension of sodium methylsulfinylmethide prepared *in situ* from a 60% dispersion of sodium hydride in mineral oil (5.00 g, 125 mmol, 2.5 equiv) and dimethyl sulfoxide (50 mL).[39] After 40 min, 4-methoxybenzyl chloride (17.0 mL, 125 mmol, 2.5 equiv) was added slowly. After 16 h, the reaction mixture was poured into ice-water (100 g). The resulting mixture was partitioned between ether (200 mL) and saturated aqueous sodium chloride solution (100 mL). The layers were separated. The aqueous layer was extracted with ether (3 × 150 mL). The organic layers were combined. The combined organic layers were washed sequentially with water (200 mL) and saturated aqueous sodium chloride solution (200 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was recrystallized from ether, affording *N,N*-bis(4-methoxybenzyl)cyanamide (**225**) as a white solid (10.5 g, 74%).

Melting Point 78–79 ºC

^{1}H NMR: 7.22 (d, 4H, J = 8.8 Hz), 6.90 (d, 4H, J = 8.8 Hz), 4.03

[38] A. Donetti, E. Bellora, *J. Org. Chem.* **1972**, *37*, 3352–3353.
[39] R. Greenwald, M. Chaykovsky, E. J. Corey, *J. Org. Chem.* **1963**, *28*, 1128–1129.

(400 MHz, $CDCl_3$)	(s, 4H), 3.81 (s, 6H).
^{13}C NMR :	159.7, 130.0, 126.3, 118.4, 114.2, 55.2, 53.5.
(100 MHz, $CDCl_3$)	
FTIR, cm^{-1}:	2959 (m), 2936 (m), 2837 (m), 2207 (s), 1611 (s), 1512
(thin film)	(vs), 1472 (m), 1246 (s), 1175 (s).
HRMS:	Calcd for $(C_{17}H_{18}N_2O_2+H)^+$ 305.1261
(ESI)	Found 305.1254
TLC	R_f = 0.38 (UV)
(2:1 hexanes–ethyl acetate)	

General Procedure to Prepare *tert*-Butyl Aldimines (20–40 mmol scale). *tert*-Butylamine (3 equiv) was added to a solution of the corresponding aldehyde (1 equiv) in benzene (1.0 M). The reaction flask was placed in an oil bath preheated to 80 ºC. After 16 h, the oil bath was removed and the reaction flask was allowed to cool to 23 ºC. Hexanes (30 equiv) were added and the resulting solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The aldimines were isolated by distillation at reduced pressure or by recrystallization from hexanes, or in some cases (so noted) were used directly without further purification. In all cases yields were 70–100%.

2-Methylbenzaldehyde *tert*-Butylimine (**192**)

A colorless oil, purified by distillation at reduced pressure, bp: 70–72 ºC, 0.5 mm Hg, 85%. Spectral data were identical to those previously reported.[40]

[40] M. A. Forth, M. B. Mitchell, S. A. C. Smith, K. Gombatz, L. Snyder, *J. Org. Chem.* **1994**, *59*, 2616–2619.

4-Fluoro-2-methylbenzaldehyde *tert*-Butylimine (**226**)

A colorless oil, purified by distillation at reduced pressure, 75% yield.

Boiling Point	79–81 ºC, 0.5 mm Hg	
^{1}H NMR: (500 MHz, $CDCl_3$)	8.51 (s, 1H), 7.87 (dd, 1H, J = 8.7, 6.4 Hz), 6.91 (app td, 1H, J = 8.5, 2.7 Hz), 6.84 (dd, 1H, J = 9.6, 2.3 Hz), 2.47 (s, 3H), 1.31 (s, 9H).	
^{19}F NMR: (470 MHz, $CDCl_3$)	–112.4 (ddd, J = 14.9, 6.9, 3.4 Hz).	
^{13}C NMR : (126 MHz, $CDCl_3$)	163.4 (d, J = 250.8 Hz), 152.3, 139.6 (d, J = 8.2 Hz), 131.3 (d, J = 2.7 Hz), 129.2 (d, J = 8.2 Hz), 116.9 (d, J = 21.1 Hz), 113.0 (d, J = 22.0 Hz), 57.4, 29.6, 19.0.	
FTIR, cm^{-1}: (thin film)	2971 (m), 1602 (m), 1495 (s), 1472 (m), 1265 (vs).	
HRMS: (ESI)	Calcd for $(C_{12}H_{16}FN+H)^+$	194.1340
	Found	194.1338
TLC (9:1 hexanes–ethyl acetate)	R_f = 0.38 (UV)	

2,4,6-Trimethylbenzaldehyde *tert*-Butylimine (**227**)

A colorless oil, purified by distillation at reduced pressure, 72% yield.

Boiling Point	102–104 ºC, 0.5 mm Hg	
^{1}H NMR: (500 MHz, $CDCl_3$)	8.54 (s, 1H), 6.87 (s, 2H), 2.36 (d, 6H, J = 1.4 Hz), 2.30 (s, 3H), 1.36 (d, 9H, J = 1.8 Hz).	
^{13}C NMR : (126 MHz, $CDCl_3$)	155.6, 137.7, 136.3, 132.5, 128.9, 57.8, 29.6, 20.9, 19.9.	
FTIR, cm^{-1}: (thin film)	2967 (s), 1638 (m), 1613 (s), 1456 (m), 1222 (s), 1204 (s).	
HRMS: (ESI)	Calcd for $(C_{14}H_{21}N+H)^+$	204.1747
	Found	204.1745
TLC (9:1 hexanes–ethyl acetate)	R_f = 0.46 (UV)	

4-Methoxy-2,5-dimethylbenzaldehyde *tert*-Butylimine (**228**)

A white solid, purified by recrystallization from hexanes.

Melting Point	67–68 ºC	
^{1}H NMR:	8.54 (s, 1 H), 7.71 (s, 1 H), 6.59 (s, 1 H), 3.84 (s, 3 H),	
(500 MHz, $CDCl_3$)	2.48 (s, 3 H), 2.22 (s, 3 H), 1.32 ppm (s, 9 H).	
^{13}C NMR :	158.9, 153.1, 136.2, 128.9, 127.2, 124.3, 111.6, 57.0,	
(126 MHz, $CDCl_3$)	55.1, 29.8, 18.9, 15.5.	
FTIR, cm^{-1}:	2967 (s), 1638 (m), 1609 (s), 1505 (s), 1260 (s), 1217	
(thin film)	(s).	
HRMS:	Calcd for $(C_{14}H_{21}NO+H)^+$	220.1696
(ESI)	Found	220.1701
TLC	R_f = 0.30 (UV)	
(9:1 hexanes–ethyl acetate)		

2-Methoxy-6-methylbenzaldehyde *tert*-Butylimine (**229**)

A pale yellow oil, purified by distillation at reduced pressure, 70% yield.

Boiling Point	138–140 ºC, 0.5 mm Hg
^{1}H NMR: (500 MHz, $CDCl_3$)	8.66 (s, 1H), 7.20 (app t, 1H, J = 8.0 Hz), 6.85 (d, 1H, J = 7.8 Hz), 6.75 (d, 1H, J = 8.2 Hz), 3.82 (s, 3H), 2.53 (s, 3H), 1.37 (s, 9H).
^{13}C NMR : (126 MHz, $CDCl_3$)	158.8, 153.4, 138.5, 129.1, 125.1, 123.6, 108.0, 57.8, 55.4, 29.6, 20.7.
FTIR, cm^{-1}: (thin film)	2970 (m), 1640 (m), 1580 (m), 1470 (m), 1263 (vs).
HRMS: (ESI)	Calcd for $(C_{13}H_{19}NO+H)^+$ 206.1539 found 206.1535
TLC (9:1 hexanes–ethyl acetate)	R_f = 0.35 (UV)

5-Chloro-2-methylbenzaldehyde *tert*-Butylimine (**216**)

A white solid, purified by recrystallization from hexanes, 80%.

Melting Point	39–40 ºC
^{1}H NMR: (500 MHz, $CDCl_3$)	8.50 (s, 1H), 7.81 (d, 1H, J = 8.2 Hz), 7.19 (dd, 1H, J = 8.2, 1.8 Hz), 7.14 (d, 1H, J = 1.8 Hz), 2.46 (s, 3H), 1.31 (s, 9H).
^{13}C NMR : (126 MHz, $CDCl_3$)	152.5, 138.8, 135.3, 133.6, 130.3, 128.5, 126.3, 57.6, 29.7, 18.9.
FTIR, cm^{-1}: (thin film)	2969 (s), 1636 (m), 1593 (s), 1479 (m), 1371 (m), 1206 (s).
HRMS: (ESI)	Calcd for $(C_{12}H_{16}ClN+H)^+$ 210.1044 Found 210.1053
TLC (9:1 hexanes–ethyl acetate)	R_f = 0.41 (UV)

2,3-Dimethylbenzaldehyde *tert*-Butylimine (**230**)

A light yellow oil, used directly without further purification, 100%.

^{1}H NMR:	8.71 (d, 1H, J = 1.8 Hz), 7.75 (d, 1H, J = 7.8 Hz), 7.24–	
(500 MHz, $CDCl_3$)	7.10 (m, 2H), 2.42 (s, 3H), 2.35 (s, 3H), 1.39 (s, 9H).	
^{13}C NMR :	154.4, 136.7, 135.4, 135.3, 131.0, 125.5, 125.0, 57.3,	
(126 MHz, $CDCl_3$)	29.6, 20.1, 14.4.	
FTIR, cm^{-1}:	2971 (m), 1638 (m), 1460 (m), 1371 (m), 1265 (vs).	
(thin film)		
HRMS:	Calcd for $(C_{13}H_{19}lN+H)^+$	190.1590
(ESI)	Found	190.1591
TLC	R_f = 0.43 (UV)	
(9:1 hexanes–ethyl acetate)		

3-Fluoro-2-methylbenzaldehyde *tert*-Butylimine (**231**)

A light orange oil, used directly without further purification, 100%.

^{1}H NMR: (500 MHz, $CDCl_3$)	8.55 (s, 1H), 7.64 (d, 1H, J = 7.8 Hz), 7.18 (app td, 1H, J = 7.9, 5.7 Hz), 7.04 (app td, 1H, J = 8.7, 1.4 Hz), 2.41 (d, 3H, J = 1.8 Hz), 1.33 (d, 9H, J = 0.9 Hz).
^{19}F NMR: (470 MHz, $CDCl_3$)	–118.1 (app dt, J = 4.9, 2.7 Hz).
^{13}C NMR : (126 MHz, $CDCl_3$)	161.2 (d, J = 246.3 Hz), 152.8 (d, J = 4.6 Hz), 137.3 (d, J = 4.6 Hz), 126.6 (d, J = 9.2 Hz), 124.2 (d, J = 16.5 Hz), 122.8 (d, J = 2.7 Hz), 116.0 (d, J = 22.0 Hz), 57.7, 29.6, 9.9 (d, J = 6.4 Hz).
FTIR, cm^{-1}: (thin film)	2970 (s), 1643 (m), 1578 (m), 1462 (s), 1270 (s), 1242 (s).

HRMS:	Calcd for $(C_{12}H_{16}FN+H)^+$	194.1340
(ESI)	Found	194.1347

TLC (9:1 hexanes–ethyl acetate)	R_f = 0.43 (UV)

2-Methyl-5-(trimethylsilyl)benzaldehyde *tert*-Butylimine (**232**)

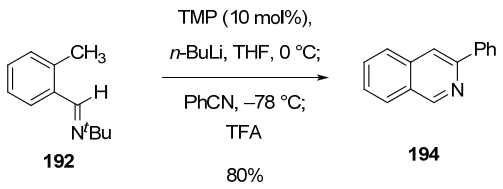
A pale yellow oil, purified by distillation at reduced pressure, 75% yield.

Boiling Point	118–120 ºC, 0.5 mm Hg.
^{1}H NMR: (500 MHz, $CDCl_3$)	8.58 (s, 1H), 7.91 (s, 1H), 7.42 (d, 1H, J = 7.3 Hz), 7.16 (d, 1H, J = 7.8 Hz), 2.49 (s, 3H), 1.31 (s, 9H), 0.27 (s, 9H).
^{13}C NMR : (126 MHz, $CDCl_3$)	154.5, 137.8, 137.7, 134.6, 134.4, 132.3, 130.1, 57.6, 29.8, 19.4, –1.1.
FTIR, cm^{-1}: (thin film)	2967 (s), 1641 (m), 1578 (m), 1472 (m), 1368 (s), 1252 (s).
HRMS: (ESI)	Calcd for $(C_{15}H_{25}NSi+H)^+$ 248.1829 Found 248.1835
TLC (9:1 hexanes–ethyl acetate)	R_f = 0.51 (UV)

3-Fluoro-5-(trimethylsilyl)benzaldehyde *tert*-Butylimine (**206**)

A light orange oil, used directly without further purification, 100%.

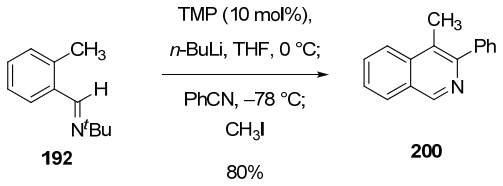
^{1}H NMR: (600 MHz, $CDCl_3$)	8.26 (d, 1H, J = 1.5 Hz), 7.53 (ddd, 1H, J = 10.0, 2.9, 1.8 Hz), 7.51 (s, 1H), 7.21 (ddd, 1H, J = 8.2, 2.6, 0.9 Hz), 1.29 (s, 9H), 0.29 (s, 9H).
^{19}F NMR: (376 MHz, $CDCl_3$)	–114.8 (dd, J = 10.0, 8.5 Hz).
^{13}C NMR : (126 MHz, $CDCl_3$)	162.9 (d, J = 240.8 Hz), 154.2 (d, J = 2.9 Hz), 143.8 (d, J = 3.7 Hz), 139.0 (d, J = 6.6 Hz), 129.3 (d, J = 2.2 Hz), 121.5 (d, J = 19.0 Hz), 113.7 (d, J = 22.0 Hz), 57.4, 29.7, –1.2.
FTIR, cm^{-1}: (thin film)	2965 (s), 1638 (m), 1360 (m), 1248 (vs), 1090 (s).
HRMS: (ESI)	Calcd for $(C_{14}H_{22}FNSi+H)^+$ 252.1578 Found 252.1586
TLC (9:1 hexanes–ethyl acetate)	R_f = 0.49 (UV)



3-Phenylisoquinoline (**194**)

A solution of *n*-butyllithium in hexanes (2.40 M, 438 μL, 1.05 mmol, 1.05 equiv) was added dropwise over 40 min to an ice-cooled solution of imine **192** (175 mg, 1.00 mmol, 1 equiv) and 2,2,6,6-tetramethylpiperidine (17 μL, 0.10 mmol, 0.1 equiv) in tetrahydrofuran (1.5 mL), forming a deep purple solution. After 30 min, the deep purple solution was transferred by cannula to a solution of benzonitrile (155 μL, 1.5 mmol, 1.5 equiv) in tetrahydrofuran (0.4 mL) at –78 ºC, forming a dark red solution. The transfer was quantitated with tetrahydrofuran (0.1 mL). After 3 min, iodomethane (125 μL, 2 mmol, 2 equiv) was added. After 30 min, trifluoroacetic acid (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate initially, grading to 15:1 hexanes–ethyl acetate), furnishing 3-phenylisoquinoline (**194**) as a pale yellow solid (164 mg, 80%), mp: 96–97 ºC. The spectral properties were identical to those previously reported.[41]

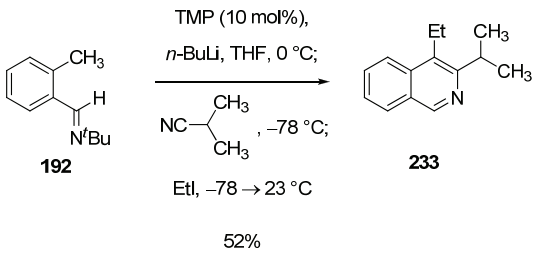
[41] H. Sard, *J. Heterocycl. Chem.* **1994**, *31*, 1085–1086.



4-Methyl-3-phenylisoquinoline (**200**)

A solution of *n*-butyllithium in hexanes (2.40 M, 424 μL, 1.02 mmol, 1.05 equiv) was added dropwise over 40 min to an ice-cooled solution of imine **192** (170 mg, 0.970 mmol, 1 equiv) and 2,2,6,6-tetramethylpiperidine (17 μL, 0.097 mmol, 0.1 equiv) in tetrahydrofuran (1.5 mL), forming a deep purple solution. After 30 min, the deep purple solution was transferred by cannula to a solution of benzonitrile (150 μL, 1.46 mmol, 1.5 equiv) in tetrahydrofuran (0.4 mL) at –78 ºC, forming a dark red solution. The transfer was quantitated with tetrahydrofuran (0.1 mL). After 3 min, iodomethane (121 μL, 1.94 mmol, 2 equiv) was added. After 30 min, trifluoroacetic acid (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate initially, grading to 10:1 hexanes–ethyl acetate, then 7:1 hexanes–ethyl acetate), furnishing 4-methyl-3-phenylisoquinoline (**200**) as a white solid (170 mg, 80%), mp: 101–102 ºC. The spectral properties were identical to those previously reported.[42]

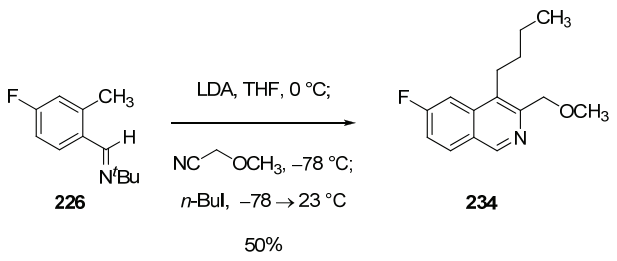
[42] K. R. Roesch, H. Zhang, R. C. Larock, *J. Org. Chem.* **1998**, *63*, 5306–5307.



4-Ethyl-3-isopropylisoquinoline (**233**)

A solution of *n*-butyllithium in hexanes (2.52 M, 616 μL, 1.55 mmol, 1.31 equiv) was added dropwise over 40 min to an ice-cooled solution of imine **192** (259 mg, 1.48 mmol, 1.25 equiv) and 2,2,6,6-tetramethylpiperidine (25 μL, 0.148 mmol, 0.125 equiv) in tetrahydrofuran (2 mL), forming a deep purple solution. After 30 min, the deep purple solution was transferred by cannula to a solution of isobutyronitrile (106 μL, 1.18 mmol, 1 equiv) in tetrahydrofuran (0.5 mL) at –78 ºC, forming a dark red solution. The transfer was quantitated with tetrahydrofuran (0.1 mL). After 5 min, iodoethane (239 μL, 2.96 mmol, 2.5 equiv) was added. After 10 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 30 min, trifluoroacetic acid (1 mL) was added. After stirring for 10 min, the reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (40:1 hexanes–ethyl acetate initially, grading to 20:1 hexanes–ethyl acetate, then 15:1 hexanes–ethyl acetate), furnishing 4-ethyl-3-isopropylisoquinoline (**233**) as a pale yellow oil (122 mg, 52%).

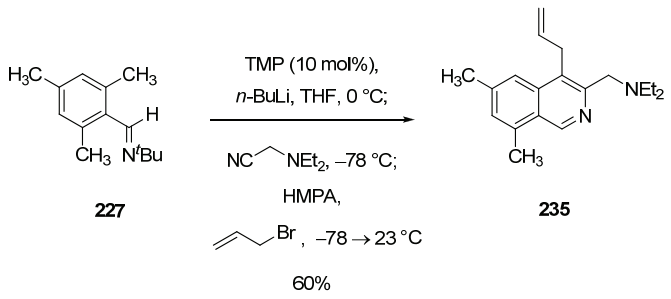
^{1}H NMR: (500 MHz, $CDCl_3$)	9.14 (s, 1H), 7.98 (d, 1H, J = 8.8 Hz), 7.89 (d, 1H, J = 8.3 Hz), 7.65 (ddd, 1H, J = 8.4, 7.0, 1.2 Hz), 7.48 (ddd, 1H, J = 8.8, 7.0, 1.2 Hz), 3.51 (spt, 1H, J = 6.7 Hz), 3.09 (q, 2H, J = 7.3 Hz), 1.38 (d, 6H, J = 6.3 Hz), 1.29 (t, 3H, J = 7.8 Hz).	
^{13}C NMR : (126 MHz, $CDCl_3$)	157.0, 150.3, 134.9, 129.8, 128.1, 127.9, 127.1, 125.5, 122.9, 30.6, 22.7, 20.4, 15.2.	
FTIR, cm^{-1}: (thin film)	2965 (s), 1620 (m), 1578 (m), 1472 (m), 1377 (m), 1246 (m).	
HRMS: (ESI)	Calcd for $(C_{14}H_{17}N+H)^+$	200.1434
	Found	200.1441
TLC (9:1 hexanes–ethyl acetate)	R_f = 0.37 (UV)	



4-*n*-Butyl-6-fluoro-3-(methoxymethyl)isoquinoline (**234**)

A solution of *n*-butyllithium in hexanes (2.50 M, 435 μL, 1.09 mmol, 1.31 equiv) was added dropwise to an ice-cooled solution of diisopropylamine (161 μL, 1.14 mmol, 1.38 equiv) in tetrahydrofuran (1.5 mL). After 15 min, a solution of imine **226** (200 mg, 1.04 mmol, 1.25 equiv) in tetrahydrofuran (0.5 mL) was added by cannula, forming a deep purple solution. After 60 min, the deep purple solution was transferred by cannula to a solution of methoxyacetonitrile (62 μL, 0.83 mmol, 1 equiv) in tetrahydrofuran (0.4 mL) at –78 ºC, forming a dark red solution. The transfer was quantitated with tetrahydrofuran (0.1 mL). After 60 min, 1-iodobutane (237 μL, 2.07 mmol, 2.5 equiv) was added. After 10 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 30 min, saturated aqueous ammonium chloride (1 mL) was added. After 10 min, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (10:1 hexanes–ethyl acetate initially, grading to 5:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate, and finally 1:1 hexanes–ethyl acetate), affording 4-butyl-6-fluoro-3-(methoxymethyl)isoquinoline (**234**) as a pale yellow oil (102 mg, 50%).

^{1}H NMR: (500 MHz, $CDCl_3$)	9.08 (s, 1H), 7.97 (dd, 1H, J = 9.0, 5.6 Hz), 7.61 (dd, 1H, J = 10.7, 2.0 Hz), 7.35 (app td, 1H, J = 8.7, 2.2 Hz), 4.77 (s, 2H), 3.49 (s, 3H), 3.05 (t, 2H, J = 7.5 Hz), 1.70–1.59 (m, 2H), 1.58–1.48 (m, 2H), 1.01 (t, 3H, J = 7.3 Hz).	
^{19}F NMR : (470 MHz, $CDCl_3$)	–107.0 (ddd, J = 11.43, 8.00, 5.71 Hz).	
^{13}C NMR : (126 MHz, $CDCl_3$)	163.4 (d, J = 250 Hz), 149.7, 148.6, 137.0 (d, J = 10.1 Hz), 131.1 (d, J = 10.1 Hz), 130.9 (d, J = 5.5 Hz), 125.4, 117.2 (d, J = 26.3 Hz), 107.2 (d, J = 21.0 Hz), 74.3, 58.6, 32.9, 27.5, 23.2, 13.9.	
FTIR, cm^{-1}: (thin film)	2957 (m), 2928 (m), 2872 (m), 1628 (s), 1501 (s), 1435 (m), 1196 (s).	
HRMS: (ESI)	Calcd for $(C_{15}H_{18}FNO+H)^+$	248.1445
	Found	248.1449
TLC (2:1 hexanes–ethyl acetate)	R_f = 0.21 (UV)	

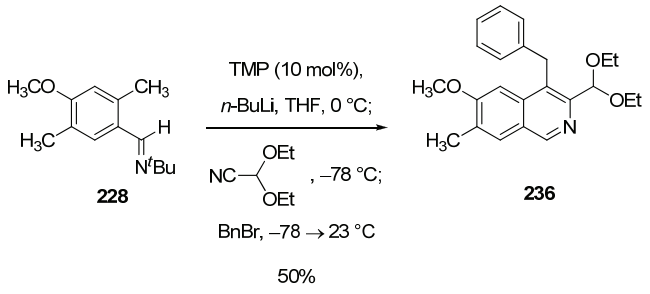


4-Allyl-6,8-dimethyl-3-(diethylaminomethyl)isoquinoline (**235**)

A solution of *n*-butyllithium in hexanes (2.50 M, 490 μL, 1.22 mmol, 1.31 equiv) was added dropwise over 40 min to an ice-cooled solution of imine **227** (237 mg, 1.17 mmol, 1.25 equiv) and 2,2,6,6-tetramethylpiperidine (20 μL, 0.117 mmol, 0.125 equiv) in tetrahydrofuran (2 mL), forming a deep purple solution. After 30 min, the deep purple solution was transferred by cannula to a solution of 2-(diethylamino)acetonitrile (121 μL, 0.866 mmol, 1 equiv) in tetrahydrofuran (0.4 mL) at –78 ºC, forming an orange solution. The transfer was quantitated with tetrahydrofuran (0.1 mL). After 5 min, hexamethylphosphoramide (406 μL, 2.33 mmol, 2.5 equiv) was added. After 10 min, allyl bromide (197 μL, 2.33 mmol, 2.5 equiv) was added. After 10 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 30 min, trifluoroacetic acid (1 mL) was added. After stirring for 10 min, the reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (2:1 hexanes–ethyl acetate initially, grading to 1:1 hexanes–ethyl acetate, then 1:1:0.01

hexanes–ethyl acetate–triethylamine), furnishing 4-allyl-6,8-dimethyl-3-(diethylaminomethyl)isoquinoline (**235**) as a pale yellow oil (158 mg, 60%).

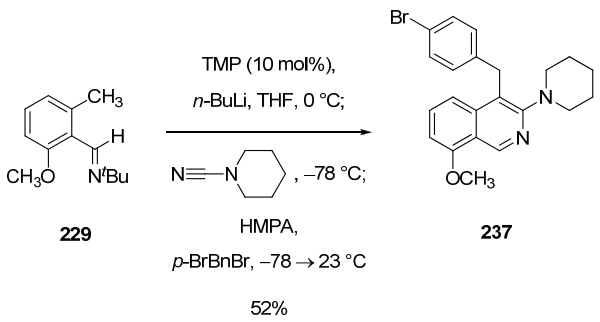
^{1}H NMR: (500 MHz, $CDCl_3$)	9.26 (s, 1H), 7.61 (s, 1H), 7.17 (s, 1H), 6.11–5.99 (m, 1H), 5.07–4.98 (m, 1H), 4.95–4.86 (m, 1H), 4.02 (app dt, 2H, J = 5.5, 1.8 Hz), 3.86 (s, 2H), 2.73 (s, 3H), 2.58 (q, 4H, J = 7.0 Hz), 2.50 (s, 3H), 1.05 (t, 6H, J = 7.1 Hz).
^{13}C NMR : (126 MHz, $CDCl_3$)	150.7, 146.5, 139.8, 136.6, 136.4, 135.4, 129.4, 127.5, 125.2, 120.5, 115.4, 58.4, 47.0, 31.1, 22.4, 18.6, 11.6.
FTIR, cm^{-1}: (thin film)	3389 (br), 2969 (s), 1622 (s), 1595 (m), 1452 (s), 1368 (s), 1200 (m).
HRMS: (ESI)	Calcd for $(C_{19}H_{26}N_2+H)^+$ 283.2169 Found 283.2170
TLC (90:9:1 dichloromethane–methanol–triethyl amine)	R_f = 0.23 (UV)



4-Benzyl-3-(diethoxymethyl)-6-methoxy-7-methylisoquinoline (**236**)

A solution of *n*-butyllithium in hexanes (2.52 M, 521 μL, 1.31 mmol, 1.31 equiv) was added dropwise over 40 min to an ice-cooled solution of imine **228** (274 mg, 1.25 mmol, 1.25 equiv) and 2,2,6,6-tetramethylpiperidine (21 μL, 0.125 mmol, 0.125 equiv) in tetrahydrofuran (2 mL), forming a deep purple solution. After 30 min, the deep purple solution was transferred by cannula to a solution of 2,2-diethoxyacetonitrile (139 μL, 1.00 mmol, 1 equiv) in tetrahydrofuran (0.4 mL) at –78 ºC, forming a dark orange solution. The transfer was quantitated with tetrahydrofuran (0.1 mL). After 5 min, benzyl bromide (371 μL, 3.13 mmol, 2.5 equiv) was added. After 10 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 30 min, trifluoroacetic acid (1 mL) was added. After stirring for 10 min, the reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (10:1 hexanes–ethyl acetate initially, grading to 5:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate), furnishing 4-benzyl-3-(diethoxymethyl)-6-methoxy-7-methylisoquinoline (**236**) as a pale yellow oil (184 mg, 50%).

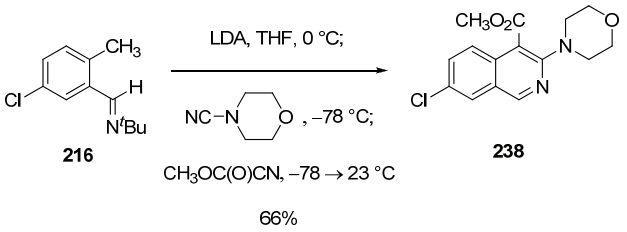
^{1}H NMR: (500 MHz, $CDCl_3$)	8.99 (s, 1H), 7.65 (s, 1H), 7.22–7.17 (m, 2H), 7.17–7.08 (m, 3H), 7.01 (s, 1H), 5.79 (s, 1H), 4.68 (s, 2H), 3.76 (dq, 2H, J = 9.4, 7.1 Hz), 3.70 (s, 3H), 3.58 (dq, 2H, J = 9.4, 7.1 Hz), 2.32 (s, 3H), 1.15 (t, 6H, J = 6.9 Hz).	
^{13}C NMR : (126 MHz, $CDCl_3$)	160.0, 149.1, 148.8, 140.9, 137.1, 129.9, 128.6, 128.3, 128.2, 126.6, 125.6, 124.2, 105.0, 101.1, 63.0, 55.2, 32.9, 16.7, 15.1.	
FTIR, cm^{-1}: (thin film)	2974 (m), 1630 (s), 1495 (s), 1418 (m), 1234 (s), 1111 (s).	
HRMS: (ESI)	Calcd for $(C_{23}H_{27}NO_3+H)^+$	366.2064
	Found	366.2076
TLC (2:1 hexanes–ethyl acetate)	R_f = 0.41 (UV)	



4-(4-Bromobenzyl)-8-methoxy-3-(piperidin-1-yl)isoquinoline (**237**)

A solution of *n*-butyllithium in hexanes (2.52 M, 436 μL, 1.10 mmol, 1.05 equiv) was added dropwise over 40 min to an ice-cooled solution of imine **229** (215 mg, 1.05 mmol, 1 equiv) and 2,2,6,6-tetramethylpiperidine (18 μL, 0.105 mmol, 0.1 equiv) in tetrahydrofuran (2 mL), forming a deep purple solution. After 30 min, the reaction flask was cooled to –78 ºC, and 1-piperidinecarbonitrile (182 μL, 1.57 mmol, 1.5 equiv) was added. After 10 min, hexamethylphosphoramide (300 μL, 1.72 mmol, 2 equiv) was added. After 10 min, a solution of 4-bromobenzyl bromide (523 mg, 2.10 mmol, 2 equiv) in tetrahydrofuran (0.5 mL) was added. After 20 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 30 min, trifluoroacetic acid (1 mL) was added. After stirring for 10 min, the reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (40:1 hexanes–ethyl acetate initially, grading to 20:1 hexanes–ethyl acetate, then 10:1 hexanes–ethyl acetate, and finally 7:1 hexanes–ethyl acetate), affording 4-(4-bromobenzyl)-8-methoxy-3-(piperidin-1-yl)isoquinoline (**237**) as a white solid (224 mg, 52%);

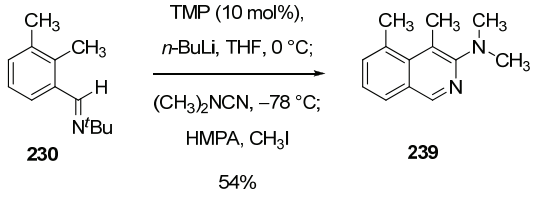
Melting Point	152–153 ºC
^{1}H NMR: (500 MHz, $CDCl_3$)	9.43 (s, 1H), 7.40 (dd, 1H, *J* = 8.5, 7.6 Hz), 7.32 (d, 2H, *J* = 8.3 Hz), 7.19 (d, 1H, *J* = 8.8 Hz), 6.98 (d, 2H, *J* = 8.3 Hz), 6.70 (d, 1H, *J* = 7.3 Hz), 4.42 (s, 2H), 4.00 (s, 3H), 3.10–2.97 (m, 4H), 1.74–1.62 (m, 4H), 1.62–1.54 (m, 2H).
^{13}C NMR : (126 MHz, $CDCl_3$)	159.6, 157.1, 145.5, 140.1, 138.7, 131.3, 130.6, 129.9, 119.4, 118.5, 118.4, 115.8, 102.8, 55.6, 52.7, 32.5, 26.5, 24.4.
FTIR, cm^{-1}: (thin film)	2934 (m), 1622 (m), 1570 (s), 1487 (m), 1391 (m), 1265 (s), 1221 (s).
HRMS: (ESI)	Calcd for $(C_{22}H_{23}BrN_2O+H)^+$ 411.1067 Found 411.1063
TLC (9:1 hexanes–ethyl acetate)	R_f = 0.26 (UV)



Methyl 7-Chloro-3-morpholinoisoquinoline-4-carboxylate (**238**)

A solution of *n*-butyllithium in hexanes (2.50 M, 420 μL, 1.05 mmol, 1.05 equiv) was added dropwise to an ice-cooled solution of diisopropylamine (155 μL, 1.10 mmol, 1.1 equiv) in tetrahydrofuran (1.5 mL). After 15 min, a solution of imine **216** (210 mg, 1.00 mmol, 1 equiv) in tetrahydrofuran (0.5 mL) was added by cannula, forming a deep purple solution. After 60 min, the reaction flask was cooled to –78 ºC, and 4-morpholinecarbonitrile (152 μL, 1.50 mmol, 1.5 equiv) was added. After 60 min, methyl cyanoformate (150 μL, 2.00 mmol, 2 equiv) was added. After 10 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 30 min, saturated aqueous ammonium chloride (1 mL) was added. After 10 min, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (10:1 hexanes–ethyl acetate initially, grading to 5:1 hexanes–ethyl acetate, then 2:1 hexanes–ethyl acetate), furnishing methyl 7-chloro-3-morpholinoisoquinoline-4-carboxylate (**238**) as a yellow oil (208 mg, 66%).

^{1}H NMR: (400 MHz, $CDCl_3$)	δ 8.89 (s, 1H), 8.00 (d, 1H, J = 1.8 Hz), 7.75 (d, 1H, J = 8.4 Hz), 7.28 (dd, 1H, J = 8.8, 1.8 Hz), 3.99 (s, 3H), 3.82–3.75 (m, 4H), 3.59–3.52 (m, 4H).	
^{13}C NMR : (100 MHz, $CDCl_3$)	168.7, 156.0, 152.7, 138.4, 137.0, 129.6, 125.0, 121.6, 104.5, 67.1, 52.2, 49.1.	
FTIR, cm^{-1}: (thin film)	2963 (m), 2857 (m), 1707 (vs), 1611 (s), 1487 (s), 1435 (s), 1215 (s), 1115 (s).	
HRMS: (ESI)	Calcd for $(C_{15}H_{15}ClN_2O_3+H)^+$	307.0844
	Found	307.0852
TLC (2:1 hexanes–ethyl acetate)	R_f = 0.41 (UV)	

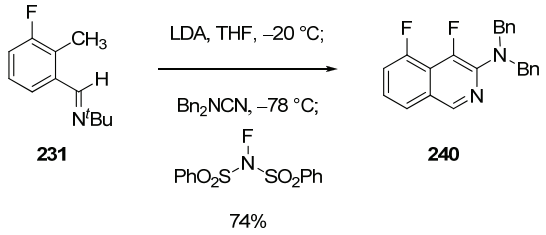


N,*N*,4,5-Tetramethylisoquinolin-3-amine (**239**)

A solution of *n*-butyllithium in hexanes (2.50 M, 422 μL, 1.05 mmol, 1.05 equiv) was added dropwise over 40 min to an ice-cooled solution of imine **230** (190 mg, 1.00 mmol, 1 equiv) and 2,2,6,6-tetramethylpiperidine (17 μL, 0.10 mmol, 0.1 equiv) in tetrahydrofuran (2 mL), forming a deep purple solution. After 30 min, the reaction flask was cooled to –78 ºC, and *N,N*-dimethylcyanamide (122 μL, 1.50 mmol, 1.5 equiv) was added, forming a dark red solution. After 15 min, hexamethylphosphoramide (349 μL, 2.00 mmol, 2 equiv) was added. After 15 min, iodomethane (125 μL, 2.00 mmol, 2 equiv) was added. After 30 min, trifluoroacetic acid (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (40:1 hexanes–ethyl acetate initially, grading to 20:1 hexanes–ethyl acetate, then 15:1 hexanes–ethyl acetate), affording *N*,*N*,4,5-tetramethylisoquinolin-3-amine (**239**) as a pale yellow oil (108 mg, 54%).

^{1}H NMR: 8.82 (s, 1H), 7.67 (d, 1H, J = 8.2 Hz), 7.35 (d, 1H, J =

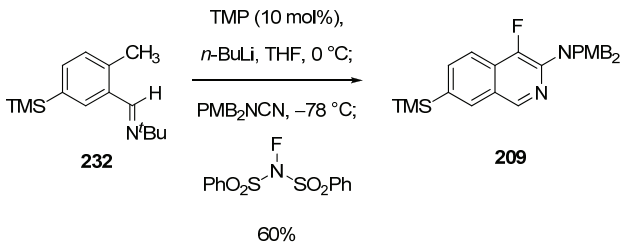
(500 MHz, $CDCl_3$)	6.9 Hz), 7.23 (dd, 1H, J = 8.0, 7.1 Hz), 2.91 (s, 6H), 2.88 (s, 3H), 2.76 (s, 3H).	
^{13}C NMR :	159.7, 149.1, 138.6, 133.9, 132.9, 126.9, 126.7, 123.8,	
(126 MHz, $CDCl_3$)	115.6, 42.9, 25.2, 19.0.	
FTIR, cm^{-1}:	2938 (m), 2861 (m), 1611 (m), 1576 (s), 1482 (s), 1400	
(thin film)	(s), 1332 (m), 1144 (m).	
HRMS:	Calcd for $(C_{13}H_{16}N_2+H)^+$	201.1386
(ESI)	Found	201.1390
TLC	R_f = 0.35 (UV)	
(9:1 hexanes–ethyl acetate)		



N,N-Dibenzyl-4,5-difluoroisoquinolin-3-amine (**240**)

A solution of *n*-butyllithium in hexanes (2.50 M, 443 μL, 1.11 mmol, 1.32 equiv) was added dropwise to a cooled solution of diisopropylamine (164 μL, 1.16 mmol, 1.37 equiv) in tetrahydrofuran (1.5 mL) at –20 ºC. After 15 min, a solution of imine **231** (204 mg, 1.06 mmol, 1.25 equiv) in tetrahydrofuran (0.5 mL) was added by cannula, forming a deep purple solution. After 60 min, the reaction flask was cooled to –78 ºC, and a solution of *N,N*-dibenzylcyanamide (293 mg, 1.32 mmol, 1.56 equiv) in tetrahydrofuran (1 mL) was added. After 60 min, a solution of *N*-fluorobenzenesulfonimide (266 mg, 0.844 mmol, 1 equiv) in tetrahydrofuran (1 mL) was added. After 10 min, trifluoroacetic acid (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. Saturated aqueous sodium carbonate solution (5 mL) was added slowly. The reaction mixture was concentrated to remove the bulk of solvent. The concentrate was partitioned between dichloromethane (60 mL) and saturated aqueous sodium carbonate solution (10 mL). The layers were separated. The organic solution was washed with water (10 mL) then saturated aqueous sodium chloride solution (10 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (40:1 hexanes–ethyl acetate initially, grading to 20:1 hexanes–ethyl acetate, then 10:1 hexanes–ethyl acetate), furnishing *N,N*-dibenzyl-4,5-difluoroisoquinolin-3-amine (**240**) as a yellow oil (226 mg, 74%).

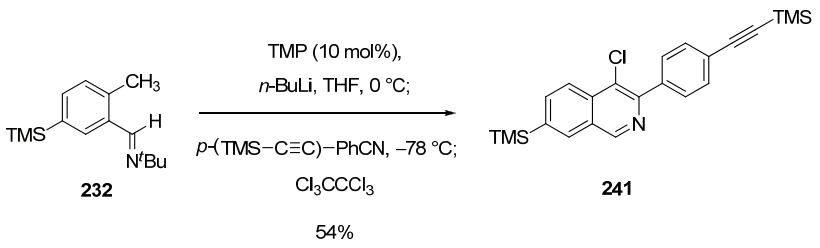
^{1}H NMR: (500 MHz, $CDCl_3$)	δ 8.78 (d, 1H, *J* = 2.3 Hz), 7.61 (ddd, 1H, *J* = 5.3, 3.9, 2.3 Hz), 7.41–7.32 (m, 8H), 7.31–7.26 (m, 2H), 7.25–7.21 (m, 2H), 4.85 (s, 4H).	
^{19}F NMR: (470 MHz, $CDCl_3$)	–118.8– –118.4 (m), –143.5 (d, *J* = 52.0 Hz).	
^{13}C NMR : (126 MHz, $CDCl_3$)	155.6 (d, *J* = 255.0 Hz), 144.9 (dd, *J* = 7.3, 1.8 Hz), 144.5 (d, *J* = 8.2 Hz), 138.9, 139.7 (dd, *J* = 259.0, 2.2 Hz), 128.4, 127.7, 127.0, 126.9, 123.5 (d, *J* = 8.2 Hz), 122.9 (d, *J* = 3.7 Hz), 119.3 (dd, *J* = 12.6, 12.0 Hz), 114.6 (dd, *J* = 20.2, 1.9 Hz), 52.7 (d, *J* = 5.5 Hz).	
FTIR, cm^{-1}: (thin film)	3028 (m), 2912 (m), 1595 (s), 1364 (s), 1244 (s), 1049 (s).	
HRMS: (ESI)	Calcd for $(C_{23}H_{18}F_2N_2 + H)^+$	361.1511
	Found	365.1510
TLC (9:1 hexanes–ethyl acetate)	R_f = 0.38 (UV)	



4-Fluoro-*N,N*-bis(4-methoxybenzyl)-7-(trimethylsilyl)isoquinolin-3-amine (**209**)

A solution of *n*-butyllithium in hexanes (2.50 M, 1.60 mL, 4.00 mmol, 1.31 equiv) was added dropwise to an ice-cooled solution of imine **232** (943 mg, 3.81 mmol, 1.25 equiv) and 2,2,6,6-tetramethylpiperidine (65 μL, 0.38 mmol, 0.125 equiv) in tetrahydrofuran (5 mL) over 60 min, forming a deep purple solution. After 30 min, the reaction flask was cooled to –78 ºC, and a solution of *N,N*-bis(4-methoxybenzyl)cyanamide (**225**) (1.35 g, 4.76 mmol, 1.56 equiv) in tetrahydrofuran (2.5 mL) was added. After 15 min, a solution of *N*-fluorobenzenesulfonimide (961 mg, 3.05 mmol, 1 equiv) in tetrahydrofuran (2 mL) was added. After 10 min, trifluoroacetic acid (3 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. Saturated aqueous sodium carbonate solution (15 mL) was added slowly. The reaction mixture was concentrated to remove the bulk of solvent. The concentrate was partitioned between dichloromethane (120 mL) and saturated aqueous sodium carbonate solution (30 mL). The layers were separated. The organic solution was washed with water (30 mL) then saturated aqueous sodium chloride solution (30 mL). The washed solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (40:1 hexanes–ethyl acetate initially, grading to 20:1 hexanes–ethyl acetate, then 15:1 hexanes–ethyl acetate), affording 4-fluoro-*N,N*-bis(4-methoxybenzyl)-7-(trimethylsilyl)isoquinolin-3-amine (**209**) as a yellow oil (863 mg, 60%).

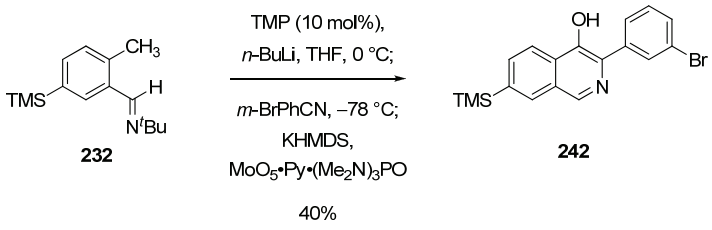
^{1}H NMR: (500 MHz, $CDCl_3$)	8.77 (s, 1H), 7.96 (s, 1H), 7.84 (d, 1H, J = 8.7 Hz), 7.68 (dd, 1H, J = 8.7, 0.9 Hz), 7.23 (d, 4H, J = 8.7 Hz), 6.84 (d, 4H, J = 8.7 Hz), 4.70 (s, 4H), 3.79 (s, 6H), 0.34 (s, 9H).
^{19}F NMR : (470 MHz, $CDCl_3$)	–148.5 (s).
^{13}C NMR : (126 MHz, $CDCl_3$)	145.5 (d, J = 5.5 Hz), 143.4 (d, J = 6.4 Hz), 141.5 (d, J = 252.7 Hz), 135.7, 134.0, 132.7, 131.1, 129.0, 128.5 (d, J = 15.6 Hz), 124.5, 117.1 (d, J = 5.5 Hz), 113.7, 55.2, 51.7 (d, J = 4.6 Hz), –1.2.
FTIR, cm^{-1}: (thin film)	2953 (m), 1732 (s), 1622 (s), 1510 (s), 1499 (s), 1246 (s).
HRMS: (ESI)	Calcd for $(C_{28}H_{31}FN_2O_2Si+H)^+$ 475.2212 Found 475.2191.
TLC (9:1 hexanes–ethyl acetate)	R_f = 0.32 (UV)



4-Chloro-7-(trimethylsilyl)-3-(4-((trimethylsilyl)ethynyl)phenyl)isoquinoline (**241**)

A solution of *n*-butyllithium in hexanes (2.52 M, 362 μL, 0.912 mmol, 1.05 equiv) was added dropwise to an ice-cooled solution of imine **232** (215 mg, 0.869 mmol, 1 equiv) and 2,2,6,6-tetramethylpiperidine (15 μL, 0.087 mmol, 0.1 equiv) in tetrahydrofuran (1.5 mL) over 40 min, forming a deep purple solution. After 30 min, the reaction flask was cooled to –78 ºC, and a solution of 4-[(trimethylsilyl)ethynyl]benzonitrile (216 mg, 1.09 mmol, 1.25 equiv) in tetrahydrofuran (0.5 mL) was added, forming a dark red solution. After 5 min, the bright red solution was transferred by cannula to a suspension of hexachloroethane (823 mg, 3.48 mmol, 4 equiv) in tetrahydrofuran (1 mL) at –78 ºC. After 15 min, trifluoroacetic acid (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (80:1 hexanes–ethyl acetate initially, grading to 60:1 hexanes–ethyl acetate, then 40:1 hexanes–ethyl acetate), furnishing 4-chloro-7-(trimethylsilyl)-3-(4-((trimethylsilyl)ethynyl)phenyl)isoquinoline (**241**) as a white solid (191 mg, 54%).

Melting Point	118–120 ºC
^{1}H NMR: (500 MHz, $CDCl_3$)	9.23 (s, 1H), 8.28 (d, 1H, J = 8.7 Hz), 8.16 (s, 1H), 7.95 (d, 1H, J = 8.2 Hz), 7.79 (d, 2H, J = 8.2 Hz), 7.61 (d, 2H, J = 8.2 Hz), 0.40 (s, 9H), 0.30 (s, 9H).
^{13}C NMR : (126 MHz, $CDCl_3$)	150.6, 149.1, 141.3, 139.0, 135.7, 134.6, 133.3, 131.5, 129.8, 127.9, 125.8, 123.1, 122.8, 105.0, 95.1, 0.0, –1.3.
FTIR, cm^{-1}: (thin film)	2957 (m), 2158 (m), 1697 (m), 1612 (m), 1568 (m), 1427 (m), 1250 (s).
HRMS: (ESI)	Calcd for $(C_{23}H_{26}ClNSi_2+H)^+$ 408.1365 Found 408.1359
TLC (9:1 hexanes–ethyl acetate)	R_f = 0.45 (UV)

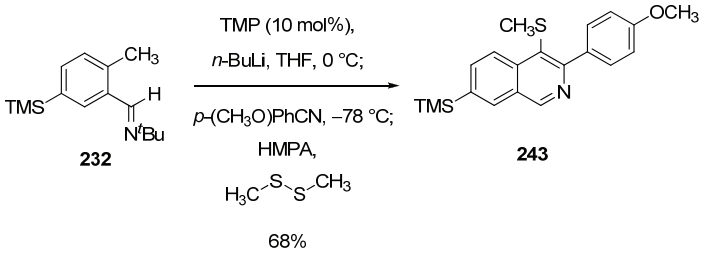


3-(3-Bromophenyl)-7-(trimethylsilyl)isoquinolin-4-ol (**242**)

A 25-mL three-neck flask was equipped with a magnetic stirrer, two rubber septa, one affixed with an argon balloon, and an L-shaped glass tube with male joints at each ends, one inserted into a side neck of the three neck reaction flask and the other wired to a 5-mL round-bottom flask containing solid oxodiperoxymolybdenum(pyridine)-(hexamethylphosphoric triamide) (MoOPH) (568 mg, 1.27 mmol, 1.5 equiv). The L-tube was angled such that its rotation would allow controlled addition of MoOPH to the reaction mixture. The three-neck flask was charged with imine **232** (210 mg, 0.849 mmol, 1 equiv), 2,2,6,6-tetramethylpiperidine (14 μL, 0.085 mmol, 0.1 equiv), and tetrahydrofuran (1.5 mL) and the resulting solution was cooled in an ice bath. A solution of *n*-butyllithium in hexanes (2.52 M, 354 μL, 0.891 mmol, 1.05 equiv) was added dropwise over a period of 40 min, forming a deep purple solution. After 30 min, the reaction flask was cooled to –78 ºC, and a solution of 3-bromobenzonitrile (193 mg, 1.06 mmol, 1.25 equiv) in tetrahydrofuran (0.5 mL) was added, forming a bright red solution. After 3 min, a solution of potassium bis(trimethylsilyl)amide (169 mg, 0.849 mmol, 1 equiv) in tetrahydrofuran (0.85 mL) was added. After another 3 min, MoOPH was added by rotating the L-tube and gently tapping the 5-mL side flask to dislodge the solids. After 60 min, trifluoroacetic acid (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between dichloromethane (30 mL) and a 1:1 mixture of saturated aqueous sodium sulfite

solution and saturated aqueous sodium carbonate solution (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 to 15:1 then 10:1 hexanes–acetone), furnishing 3-(3-bromophenyl)-7-(trimethylsilyl)isoquinolin-4-ol (**241**) as a white solid (126 mg, 40%).

Melting Point	215–217 ºC	
^{1}H NMR: (500 MHz, $CDCl_3$)	8.91 (s, 1H), 8.18 (d, 1H, *J* = 8.4 Hz), 8.11 (s, 1H), 7.96 (app t, 1H, *J* = 1.6 Hz), 7.85 (dd, 1H, *J* = 8.2, 0.9 Hz), 7.72 (ddd, 1H, *J* = 7.7, 1.2, 1.0 Hz), 7.53 (app dt, 1H, *J* = 8.1, 1.3 Hz), 7.37 (app t, 1H, *J* = 7.9 Hz), 6.10 (br s, 1H), 0.38 (s, 9H).	
^{13}C NMR : (126 MHz, $CDCl_3$)	145.0, 144.1, 141.0, 139.2, 134.7, 134.0, 132.8, 132.1, 131.5, 130.7, 128.7, 127.8, 127.3, 123.6, 120.2, –1.2.	
FTIR, cm^{-1}: (thin film)	2951 (m), 1728 (m), 1576 (m), 1557 (s), 1346 (s), 1327 (s), 1250 (s).	
HRMS: (ESI)	Calcd for $(C_{18}H_{18}BrNOSi+H)^+$	372.0414
	Found	372.0427
TLC (10:1 hexanes–acetone)	R_f = 0.19 (UV)	

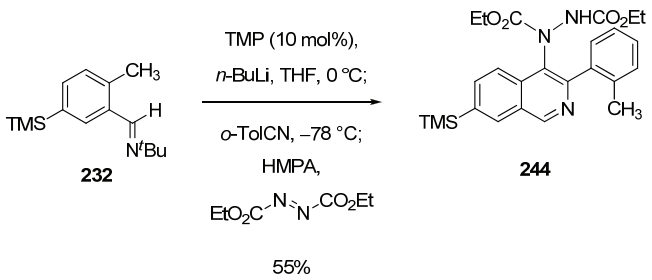


3-(4-Methoxyphenyl)-4-(methylthio)-7-(trimethylsilyl)isoquinoline (**243**)

A solution of *n*-butyllithium in hexanes (2.52 M, 330 μL, 0.832 mmol, 1.05 equiv) was added dropwise over 40 min to an ice-cooled solution of imine **232** (196 mg, 0.792 mmol, 1 equiv) and 2,2,6,6-tetramethylpiperidine (14 μL, 0.079 mmol, 0.1 equiv) in tetrahydrofuran (1.5 mL), forming a deep purple solution. After 30 min, the reaction flask was cooled to –78 ºC, and a solution of 4-methoxybenzonitrile (158 mg, 1.19 mmol, 1.5 equiv) in tetrahydrofuran (0.5 mL) was added, forming a dark red solution. After 10 min, hexamethylphosphoramide (276 μL, 1.58 mmol, 2 equiv) was added. After 5 min, dimethyl disulfide (140 μL, 1.58 mmol, 2 equiv) was added. After 30 min, trifluoroacetic acid (1 mL) was added. The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate initially, grading to 10:1 hexanes–ethyl acetate, then 7:1 hexanes–ethyl acetate), affording 3-(4-methoxyphenyl)-4-(methylthio)-7-(trimethylsilyl)isoquinoline (**243**) as a white solid (190 mg, 68%).

Melting Point 122–124 ºC

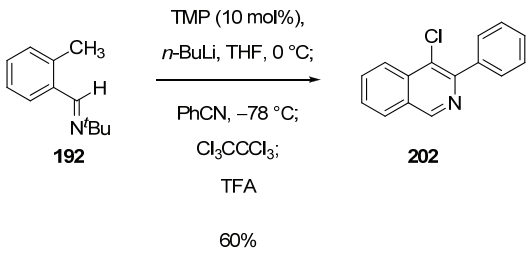
^{1}H NMR: (500 MHz, $CDCl_3$)	9.25 (s, 1H), 8.58 (d, 1H, J = 7.8 Hz), 8.15 (s, 1H), 7.94 (dd, 1H, J = 8.2, 1.4 Hz), 7.74 (d, 2H, J = 8.7 Hz), 7.02 (d, 2H, J = 8.7 Hz), 3.88 (s, 3H), 2.16 (s, 3H), 0.39 (s, 9H).	
^{13}C NMR : (126 MHz, $CDCl_3$)	159.5, 156.3, 152.0, 139.9, 138.2, 135.2, 133.9, 133.6, 131.3, 127.2, 125.8, 124.6, 113.2, 55.3, 19.4, –1.2.	
FTIR, cm^{-1}: (thin film)	2953 (m), 1605 (s), 1512 (s), 1418 (s), 1246 (s), 1175 (s), 1096 (m), 1034 (m).	
HRMS: (ESI)	Calcd for $(C_{20}H_{23}NOSSi+H)^+$	354.1342
	Found	354.1339
TLC (4:1 hexanes–acetone)	R_f = 0.38 (UV)	



Diethyl 1-(3-*o*-Tolyl-7-(trimethylsilyl)isoquinolin-4-yl)hydrazine-1,2-dicarboxylate (**244**)

A solution of *n*-butyllithium in hexanes (2.52 M, 269 μL, 0.679 mmol, 1.05 equiv) was added dropwise over 40 min to an ice-cooled solution of imine **232** (160 mg, 0.647 mmol, 1 equiv) and 2,2,6,6-tetramethylpiperidine (11 μL, 0.065 mmol, 0.1 equiv) in tetrahydrofuran (1.4 mL), forming a deep purple solution. After 30 min, the reaction flask was cooled to –78 ºC, and *o*-tolunitrile (115 μL, 0.97 mmol, 1.5 equiv) was added, forming a dark red solution. After 15 min, hexamethylphosphoramide (203 μL, 1.29 mmol, 2 equiv) was added. After 15 min, diethyl azodicarboxylate (203 μL, 1.29 mmol, 2 equiv) was added. After 30 min, trifluoroacetic acid (1 mL) was added. The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate initially, grading to 10:1 hexanes–ethyl acetate, then 5:1 hexanes–ethyl acetate, and finally 3:1 hexanes–ethyl acetate), affording diethyl 1-(3-*o*-tolyl-7-(trimethylsilyl)isoquinolin-4-yl)hydrazine-1,2-dicarboxylate (**244**) as a yellow oil (165 mg, 55%).

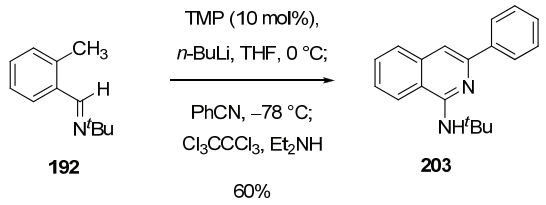
^{1}H NMR: (500 MHz, $CDCl_3$)	(observed as two rotamers in the ratio of 2:1, asterisk denotes minor rotamer peaks) 9.30 (s, 1H), 8.53 (br s, 1H), 8.19 (s, 1H), 7.96 (br s, 1H), 7.44–7.12 (br m, 5H), 6.08 (br s, 1H), 4.41–3.94 (br m, 4H), 2.18* (br s, 3H), 2.15 (br s, 3H), 1.35–1.01 (br m, 6H), 0.39 (s, 9H), 0.36* (s, 9H).	
^{13}C NMR : (126 MHz, $CDCl_3$)	(observed as two rotamers in the ratio of 2:1, asterisk denotes minor rotamer peaks) 156.1, 155.5, 152.5, 140.7, 138.0, 136.8, 135.3, 135.1, 134.2, 133.0, 131.4, 131.1, 131.0, 128.9, 128.0, 126.1, 122.8, 122.7*, 63.2, 63.0*, 62.2, 62.0*, 19.5, 14.6*, 14.5*, 14.4, 14.3, –1.2, –1.3*.	
FTIR, cm^{-1}: (thin film)	3391 (br), 2957 (m), 1728 (vs), 1479 (m), 1373 (m), 1323 (s), 1248 (s), 1223 (vs), 1096 (s), 1057 (s).	
HRMS: (ESI)	Calcd for $(C_{25}H_{31}N_3O_4Si+H)^+$	466.2157
	Found	466.2168
TLC (4:1 hexanes–acetone)	R_f = 0.20 (UV)	



4-Chloro-3-phenylisoquinoline (**202**)

A solution of *n*-butyllithium in hexanes (2.40 M, 438 μL, 1.05 mmol, 1.05 equiv) was added dropwise to an ice-cooled solution of imine **192** (175 mg, 1.00 mmol, 1 equiv) and 2,2,6,6-tetramethylpiperidine (17 μL, 0.10 mmol, 0.1 equiv) in tetrahydrofuran (1.5 mL) over 40 min, forming a deep purple solution. After 30 min, the reaction flask was cooled to –78 ºC, and benzonitrile (129 μL, 1.25 mmol, 1.25 equiv) was added, forming a dark red solution. After 5 min, the bright red solution was transferred by cannula to a suspension of hexachloroethane (710 mg, 3.00 mmol, 3 equiv) in tetrahydrofuran (1 mL) at –78 ºC. After 10 min, trifluoroacetic acid (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (40:1 hexanes–ethyl acetate initially, grading to 20:1 hexanes–ethyl acetate, then 10:1 hexanes–ethyl acetate), furnishing 4-chloro-3-phenylisoquinoline (**202**) as a yellow oil (143 mg, 60%) with spectral properties identical to those previously reported.[43]

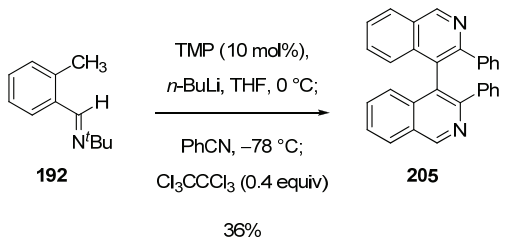
[43] X. Yu, J. Wu, *J. Comb. Chem.* **2009**, *11*, 895–899.



N-tert-Butyl-3-phenylisoquinolin-1-amine (**203**)

A solution of *n*-butyllithium in hexanes (2.40 M, 225 μL, 0.539 mmol, 1.05 equiv) was added dropwise to an ice-cooled solution of imine **192** (90 mg, 0.513 mmol, 1 equiv) and 2,2,6,6-tetramethylpiperidine (9 μL, 0.051 mmol, 0.1 equiv) in tetrahydrofuran (1 mL) over 40 min, forming a deep purple solution. After 30 min, the reaction flask was cooled to –78 ºC, and benzonitrile (66 μL, 0.642 mmol, 1.25 equiv) was added, forming a dark red solution. After 5 min, the bright red solution was transferred by cannula to a suspension of hexachloroethane (487 mg, 2.05 mmol, 4 equiv) and diethylamine (212 μL, 2.05 mmol, 4 equiv) in tetrahydrofuran (0.5 mL) at –78 ºC. After 30 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (50:1 hexanes–ethyl acetate). The product fractions were collected and concentrated. The residue (a yellow solid) was further purified by recrystallization from hexanes, furnishing *N-tert*-butyl-3-phenylisoquinolin-1-amine (**203**) as a white solid (85 mg, 60%).

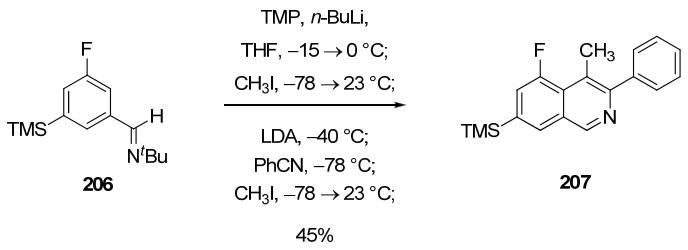
Melting Point	96–97 ºC	
^{1}H NMR: (500 MHz, $CDCl_3$)	8.22 (d, 2H, J = 8.7 Hz), 7.78–7.69 (m, 2H), 7.57 (app t, 1H, J = 7.3 Hz), 7.51 (app t, 2H, J = 7.8 Hz), 7.45 (s, 1H), 7.45–7.38 (m, 2H), 5.22 (br s, 1H), 1.71 (s, 9H).	
^{13}C NMR : (126 MHz, $CDCl_3$)	154.0, 148.7, 140.4, 138.0, 129.3, 128.4, 127.9, 127.8, 126.6, 125.4, 121.3, 117.8, 106.0, 51.8, 29.2.	
FTIR, cm^{-1}: (thin film)	3457 (m), 3059 (m), 2961 (m), 1568 (s), 1518 (vs), 1425 (s), 1323 (s), 1213 (s).	
HRMS: (ESI)	Calcd for $(C_{19}H_{20}N_2+H)^+$	277.1699
	Found	277.1700
TLC (9:1 hexanes–ethyl acetate)	R_f = 0.46 (UV)	



3,3'-Diphenyl-4,4'-bisisoquinoline (**205**)

A solution of *n*-butyllithium in hexanes (2.40 M, 438 μL, 1.05 mmol, 1.05 equiv) was added dropwise to an ice-cooled solution of imine **192** (175 mg, 1.00 mmol, 1 equiv) and 2,2,6,6-tetramethylpiperidine (17 μL, 0.10 mmol, 0.1 equiv) in tetrahydrofuran (1.5 mL) over 40 min, forming a deep purple solution. After 30 min, the deep purple solution was transferred by cannula to a solution of benzonitrile (129 μL, 1.25 mmol, 1.25 equiv) in tetrahydrofuran (0.4 mL) at –78 ºC, forming a dark red solution. The transfer was quantitated with tetrahydrofuran (0.1 mL). After 3 min, a solution of hexachloroethane (95 mg, 0.40 mmol, 0.4 equiv) in tetrahydrofuran (1 mL) was added dropwise over 5 min. After 60 min, trifluoroacetic acid (1 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate initially, grading to 10:1 hexanes–ethyl acetate, then 5:1 hexanes–ethyl acetate, and finally 3:1 hexanes–ethyl acetate), furnishing 3,3'-diphenyl-4,4'-bisisoquinoline (**205**) as a yellow solid (74 mg, 36%).

Melting Point	228–230 ºC	
^{1}H NMR: (500 MHz, $CDCl_3$)	9.40 (s, 1H), 8.12 (d, 1H, J = 8.3 Hz), 7.65 (app td, 1H, J = 8.0, 1.2 Hz), 7.59 (app td, 1H, J = 7.8, 1.2 Hz), 7.41 (d, 1H, J = 8.3 Hz), 7.07 (t, 1H, J = 7.9 Hz), 6.93 (app t, 2H, J = 7.8 Hz), 6.67 (dd, 2H, J = 8.0, 1.5 Hz).	
^{13}C NMR : (126 MHz, $CDCl_3$)	152.5, 152.2, 139.9, 137.2, 131.1, 128.9, 128.1, 127.3, 127.2, 127.1, 126.8, 125.7, 125.6.	
FTIR, cm^{-1}: (thin film)	3059 (m), 3026 (m), 1618 (s), 1576 (m), 1559 (s), 1497 (s), 1449 (s), 1250 (s).	
HRMS: (ESI)	Calcd for $(C_{30}H_{20}N_2+H)^+$	409.1699
	Found	409.1706
TLC (4:1 hexanes–ethyl acetate)	R_f = 0.17 (UV)	



5-Fluoro-4-methyl-3-phenyl-7-(trimethylsilyl)isoquinoline (**207**)

A solution of *n*-butyllithium in hexanes (2.32 M, 436 μL, 1.01 mmol, 1.17 equiv) was added to a cooled solution of 2,2,6,6-tetramethylpiperidine (181 μL, 1.06 mmol, 1.23 equiv) in tetrahydrofuran (1 mL) at –15 ºC. After 20 min, a solution of imine **206** (242 mg, 0.963 mmol, 1.11 equiv) in tetrahydrofuran (0.5 mL) was added by cannula, forming a dark green mixture. The reaction mixture was allowed to warm to 0 ºC over 90 min. The reaction flask was then cooled to –78 ºC, and iodomethane (54 μL, 0.866 mmol, 1 equiv) was added. After 15 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 1 h, the reaction flask was cooled to –40 ºC, and a freshly prepared solution of lithium diisopropylamide (1.01 mmol, 1.17 equiv) in tetrahydrofuran (1.0 mL) was added by cannula, forming a dark red solution. After 60 min, the reaction flask was cooled to –78 ºC, and benzonitrile (124 μL, 1.20 mmol, 1.39 equiv) was added. After 30 min, iodomethane (120 μL, 1.93 mmol, 2.23 equiv) was added. After 10 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 30 min, trifluoroacetic acid (1 mL) was added. The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (40:1 to

20:1 finally 10:1 hexanes–ethyl acetate), furnishing 5-fluoro-4-methyl-3-phenyl-7-(trimethylsilyl)isoquinoline (**207**) as a light yellow solid (120 mg, 45%).

Melting Point 95–96 ºC

^{1}H NMR: (500 MHz, $CDCl_3$) 9.15 (d, 1H, J = 2.3 Hz), 7.90 (s, 1H), 7.56 (app dt, 2H, J = 6.9, 1.8 Hz), 7.51–7.46 (m, 2H), 7.46 (dd, 1H, J = 13.3, 1.0 Hz), 7.41 (app tt, 1H, J = 7.8, 1.4 Hz), 2.77 (d, 3H, J = 6.4 Hz), 0.38 (s, 9H).

^{19}F NMR: (470 MHz, $CDCl_3$) –113.6– –113.5 (m).

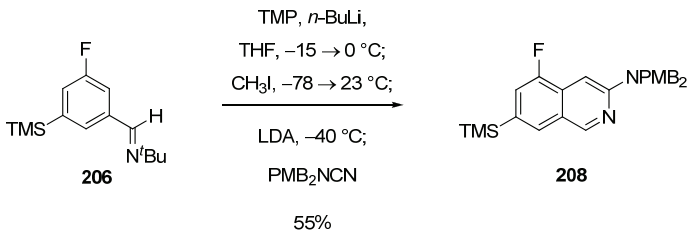
^{13}C NMR : (126 MHz, $CDCl_3$) 159.1 (d, J = 258.2 Hz), 153.4, 149.6 (d, J = 1.8 Hz), 141.0, 140.9 (d, J = 4.6 Hz), 129.8, 129.7 (d, J = 4.6 Hz), 129.4 (d, J = 3.7 Hz), 128.1, 127.7, 126.9 (d, J = 12.8 Hz), 122.6 (d, J = 4.6 Hz), 119.1 (d, J = 21.1 Hz), 18.7 (d, J = 11.0 Hz), –1.3.

FTIR, cm^{-1}: (thin film) 2955 (m), 1568 (m), 1343 (m), 1248 (s).

HRMS:	Calcd for $(C_{19}H_{20}FNSi+H)^+$	310.1422
(ESI)	Found	310.1420

TLC R_f = 0.29 (UV)

(9:1 hexanes–ethyl acetate)

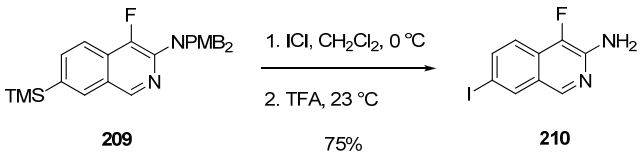


5-Fluoro-*N,N*-bis(4-methoxybenzyl)-7-(trimethylsilyl)isoquinolin-3-amine (**208**)

A solution of *n*-butyllithium in hexanes (2.50 M, 910 μL, 2.28 mmol, 1.17 equiv) was added to a cooled solution of 2,2,6,6-tetramethylpiperidine (407 μL, 2.39 mmol, 1.23 equiv) in tetrahydrofuran (3 mL) at –15 ºC. After 20 min, a solution of imine **206** (545 mg, 2.17 mmol, 1.11 equiv) in tetrahydrofuran (1 mL) was added by cannula, forming a dark green mixture. The reaction mixture was allowed to warm to 0 ºC over 90 min. The reaction flask was then cooled to –78 ºC, and iodomethane (122 μL, 1.95 mmol, 1 equiv) was added. After 15 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 1 h, the reaction flask was cooled to –40 ºC, and a freshly prepared solution of lithium diisopropylamide (2.28 mmol, 1.17 equiv) in tetrahydrofuran (2.0 mL) was added by cannula, forming a dark red solution. After 60 min, a solution of *N,N*-bis(4-methoxybenzyl)cyanamide (**225**) (826 mg, 2.93 mmol, 1.5 equiv) in tetrahydrofuran (2 mL) was added. After 40 min, trifluoroacetic acid (2 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. The reaction mixture was partitioned between saturated aqueous sodium carbonate solution (30 mL) and dichloromethane (50 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 40 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (40:1 hexanes–ethyl acetate initially, grading to 20:1 hexanes–ethyl

acetate, then 15:1 hexanes–ethyl acetate), furnishing 5-fluoro-*N,N*-bis(4-methoxybenzyl)-7-(trimethylsilyl)isoquinolin-3-amine (**208**) as a yellow oil (506 mg, 55%).

^{1}H NMR: (500 MHz, $CDCl_3$)	8.98 (s, 1H), 7.70 (s, 1H), 7.21 (d, 1H, J = 12.7 Hz), 7.20 (d, 4H, J = 8.7 Hz), 6.85 (d, 4H, J = 8.7 Hz), 6.77 (s, 1H), 4.83 (s, 4H), 3.80 (s, 6H), 0.33 (s, 9H).
^{19}F NMR: (470 MHz, $CDCl_3$)	–128.2 (d, J = 12.7 Hz).
^{13}C NMR : (126 MHz, $CDCl_3$)	158.7, 155.9, 156.5 (d, J = 253.0 Hz), 151.2 (d, J = 2.7 Hz), 133.5 (d, J = 2.7 Hz), 130.2, 130.0 (d, J = 17.4 Hz), 129.0 (d, J = 3.7 Hz), 128.4, 124.0 (d, J = 5.5 Hz), 116.2 (d, J = 16.5 Hz), 114.0, 89.3 (d, J = 4.6 Hz), 55.2, 50.5, –1.2.
FTIR, cm^{-1}: (thin film)	2953 (m), 2835 (m), 1626 (m), 1589 (s), 1510 (s), 1246 (s).
HRMS: (ESI)	Calcd for $(C_{28}H_{31}FN_2O_2Si+H)^+$ 475.2212 Found 475.2206
TLC (9:1 hexanes–ethyl acetate)	R_f = 0.30 (UV)



209 **210**

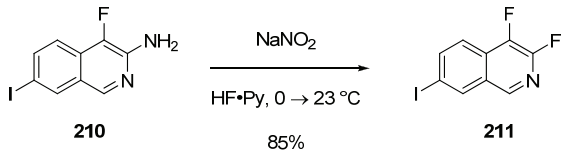
4-Fluoro-7-iodoisoquinolin-3-amine (**210**)

A solution of iodine monochloride in dichloromethane (1.0 M, 1.81 mL, 1.81 mmol, 2 equiv) was added slowly over 5 min to an ice-cooled solution of 4-fluoro-*N,N*-bis(4-methoxybenzyl)-7-(trimethylsilyl)isoquinolin-3-amine (**208**) (430 mg, 0.906 mmol, 1 equiv) in dichloromethane (5 mL). After 60 min, saturated aqueous sodium thiosulfate solution (5 mL) was added. The cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 10 min, the reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 30 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was filtered through silica gel (eluting with 7:1 hexanes–ethyl acetate) and the filtrate was concentrated. The solid residue was transformed directly in the following step.

Trifluoroacetic acid (5 mL) was added to the solid residue prepared above, forming a bright red solution. After 60 min, the reaction mixture was partitioned between saturated aqueous sodium carbonate solution (40 mL) and dichloromethane (40 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 30 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate initially, grading

to 10:1 hexanes–ethyl acetate, then 5:1 hexanes–ethyl acetate), furnishing 4-fluoro-7-iodoisoquinolin-3-amine (**210**) as a yellow solid (196 mg, 75%).

^{1}H NMR: (500 MHz, $CDCl_3$)	8.58 (s, 1H), 8.19 (app t, 1H, J = 1.6 Hz), 7.78 (dd, 1H, J = 8.9, 1.6 Hz), 7.58 (d, 1H, J = 9.2 Hz), 4.58 (br s, 2H).
^{19}F NMR: (470 MHz, $CDCl_3$)	–156.8 (d, J = 2.4 Hz).
^{13}C NMR : (126 MHz, $CDCl_3$)	144.8 (d, J = 7.3 Hz), 142.4 (d, J = 12.8 Hz), 138.8, 139.2 (d, J = 250.0 Hz), 135.9 (d, J = 1.8 Hz), 126.1, 125.8 (d, J = 12.8 Hz), 119.4 (d, J = 3.7 Hz), 87.5.
FTIR, cm^{-1}: (thin film)	3383 (m), 3263 (m), 3160 (s), 2940 (m), 1732 (s), 1645 (s), 1584 (s), 1466 (s), 1261 (s).
HRMS: (ESI)	Calcd for $(C_9H_6FIN_2+H)^+$ 288.9633 Found 288.9642
TLC (4:1 hexanes–ethyl acetate)	R_f = 0.16 (UV)



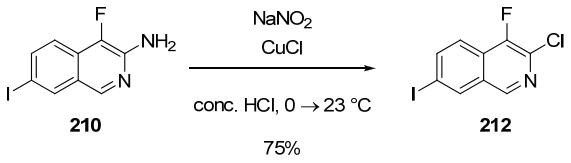
3,4-Difluoro-7-iodoisoquinoline (**211**)

A solution of sodium nitrite (25 mg, 0.365 mmol, 5 equiv) in water (0.5 mL) was added dropwise to an ice-cooled suspension of 4-fluoro-7-iodoisoquinolin-3-amine (**210**) (21 mg, 0.073 mmol, 1 equiv) in hydrogen fluoride pyridine (70% HF, 1 mL) in a Teflon reaction vessel over 5 min. After 30 min, the cooling bath was removed and the reaction vessel was allowed to warm to 23 ºC. After 60 min, saturated aqueous sodium carbonate solution (15 mL) was added slowly (CAUTION: gas evolution). The reaction mixture was then partitioned between saturated aqueous sodium chloride (15 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 15 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate), affording 3,4-difluoro-7-iodoisoquinoline (**211**) as a white solid (18 mg, 85%).

Melting Point 135–136 ºC

^{1}H NMR: (500 MHz, $CDCl_3$) 8.63 (s, 1H), 8.40 (s, 1H), 7.99 (d, 1H, J = 8.8 Hz), 7.84 (d, 1H, J = 8.8 Hz).

^{19}F NMR:	–97.3 (d, J = 20.7 Hz), –154.6 (d, J = 20.7 Hz).	
(470 MHz, $CDCl_3$)		
^{13}C NMR :	147.8 (dd, J = 235.0, 13.7 Hz), 143.2 (dd, J = 13.7, 7.7	
(126 MHz, $CDCl_3$)	Hz), 139.7, 139.2 (dd, J = 262.0, 26.4 Hz), 135.9, 130.0	
	(d, J = 2.6 Hz), 128.1 (dd, J = 12.8, 2.6 Hz), 121.0 (dd, J	
	= 7.3, 3.0 Hz), 92.4 (d, J = 2.6 Hz).	
FTIR, cm^{-1}:	3055 (m), 2930 (m), 1732 (s), 1626 (s), 1591 (s), 1442	
(thin film)	(s), 1263 (s).	
HRMS:	Calcd for $(C_9H_4F_2IN+H)^+$	291.9429
(ESI)	Found	291.9429
TLC	R_f = 0.48 (UV)	
(9:1 hexanes–ethyl acetate)		



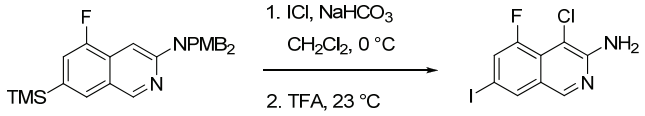
3-Chloro-4-fluoro-7-iodoisoquinoline (**212**)

A solution of sodium nitrite (53 mg, 0.764 mmol, 5 equiv) in water (0.5 mL) was added dropwise to an ice-cooled suspension of 4-fluoro-7-iodoisoquinolin-3-amine (**210**) (44 mg, 0.153 mmol, 1 equiv) in concentrated aqueous hydrochloric acid solution (37 wt %, 1.5 mL) over 5 min. After 15 min, a solution of copper(I) chloride (76 mg, 0.764 mmol, 5 equiv) in concentrated aqueous hydrochloric acid solution (37 wt %, 0.5 mL) was added dropwise over 5 min. After 30 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 60 min, the reaction mixture was partitioned between aqueous ammonium hydroxide solution (30 wt%, 10 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 15 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes(ethyl acetate), affording 3-chloro-4-fluoro-7-iodoisoquinoline (**212**) as a white solid (35 mg, 75%).

Melting Point 145–147 ºC

^{1}H NMR: (500 MHz, $CDCl_3$) 8.81 (s, 1H), 8.41 (s, 1H), 8.04 (dd, 1H, J = 8.8, 1.0 Hz), 7.81 (d, 1H, J = 8.8 Hz).

^{19}F NMR:	–131.2 (s).	
(470 MHz, $CDCl_3$)		
^{13}C NMR :	150.2 (d, J = 264.0 Hz), 145.8 (d, J = 7.3 Hz), 140.1,	
(126 MHz, $CDCl_3$)	135.9 (d, J = 1.8 Hz), 131.3 (d, J = 18.3 Hz), 130.5,	
	126.3 (d, J = 15.6 Hz), 121.0 (d, J = 2.7 Hz), 93.8.	
FTIR, cm^{-1}:	2930 (m), 1734 (s), 1578 (m), 1406 (s), 1217 (m), 1153	
(thin film)	(m).	
HRMS:	Calcd for $(C_9H_4ClFIN+H)^+$	307.9134
(ESI)	Found	307.9125
TLC	R_f = 0.43 (UV)	
(9:1 hexanes–ethyl acetate)		



208 **213**

4-Chloro-5-fluoro-7-iodoisoquinolin-3-amine (**213**)

A solution of iodine monochloride in dichloromethane (1.0 M, 1.66 mL, 1.66 mmol, 2 equiv) was added slowly over 5 min to an ice-cooled suspension of 5-fluoro-*N,N*-bis(4-methoxybenzyl)-7-(trimethylsilyl)isoquinolin-3-amine (**208**) (395 mg, 0.832 mmol, 1 equiv) and sodium bicarbonate (210 mg, 2.50 mmol, 3 equiv) in dichloromethane (5 mL). After 2 h, a second portion of iodine monochloride solution (1.0 M in dichloromethane, 0.42 mL, 0.416 mmol, 0.5 equiv) was added. After 60 min, saturated aqueous sodium thiosulfate solution (5 mL) was added. After 10 min, the reaction mixture was partitioned between saturated aqueous sodium carbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 30 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was filtered through silica gel (eluting with 7:1 hexanes–ethyl acetate) and the filtrate was concentrated. The solid residue was transformed directly in the following step.

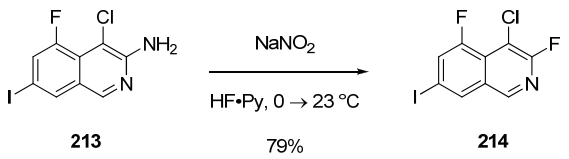
Trifluoroacetic acid (5 mL) was added to the solid residue prepared above, forming a bright red solution. After 60 min, the reaction mixture was partitioned between saturated aqueous sodium carbonate solution (40 mL) and dichloromethane (40 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 30 mL). The organic layers were combined. The combined solution was dried over sodium

sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate initially, grading to 10:1 hexanes–ethyl acetate, then 5:1 hexanes–ethyl acetate), furnishing 4-chloro-5-fluoro-7-iodoisoquinolin-3-amine (**213**) as a yellow solid (174 mg, 65%).

^{1}H NMR: (500 MHz, $CDCl_3$)	8.64 (d, 1H, J = 2.3 Hz), 7.95 (s, 1H), 7.50 (dd, 1H, J = 11.7, 1.6 Hz), 5.11 (br s, 2H).
^{19}F NMR: (470 MHz, $CDCl_3$)	–115.5 (d, J = 12.7 Hz).
^{13}C NMR : (126 MHz, $CDCl_3$)	155.5 (d, J = 262.9 Hz), 152.4, 148.5 (d, J = 1.8 Hz), 133.0 (d, J = 5.0 Hz), 127.7 (d, J = 3.7 Hz), 125.3 (d, J = 10.0 Hz), 124.8 (d, J = 23.9 Hz), 101.6, 84.0 (d, J = 7.3 Hz).
FTIR, cm^{-1}: (thin film)	3412 (m), 3291 (s), 3175 (s), 2934 (m), 1734 (s), 1634 (s), 1582 (s), 1460 (s), 1319 (s), 1234 (s).

HRMS: (ESI)	Calcd for $(C_9H_5ClFIN_2+H)^+$	322.9243
	Found	322.9255

TLC R_f = 0.24 (UV)
(4:1 hexanes–ethyl acetate)



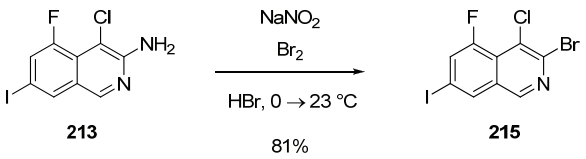
4-Chloro-3,5-difluoro-7-iodoisoquinoline (**214**)

A solution of sodium nitrite (21 mg, 0.310 mmol, 5 equiv) in water (0.5 mL) was added dropwise to an ice-cooled suspension of 4-chloro-5-fluoro-7-iodoisoquinolin-3-amine (**213**) (20 mg, 0.062 mmol, 1 equiv) in hydrogen fluoride pyridine (70% HF, 1 mL) in a Teflon reaction vessel over 5 min. After 30 min, the cooling bath was removed and the reaction vessel was allowed to warm to 23 ºC. After 60 min, saturated aqueous sodium carbonate solution (15 mL) was added slowly (CAUTION: gas evolution). The reaction mixture was then partitioned between saturated aqueous sodium chloride (15 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 15 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate), affording 4-chloro-3,5-difluoro-7-iodo isoquinoline (**214**) as a white solid (16 mg, 79%).

Melting Point 151–153 ºC

^{1}H NMR: (500 MHz, $CDCl_3$) δ 8.75 (d, 1H, *J* = 1.4 Hz), 8.20 (s, 1H), 7.71 (dd, 1H, *J* = 11.4, 0.9 Hz).

^{19}F NMR:	–76.5 (d, J = 5.7 Hz), –112.9 (dd, J = 11.4, 6.9 Hz).	
(470 MHz, $CDCl_3$)		
^{13}C NMR :	157.4 (d, J = 234.4 Hz), 156.7 (dd, J = 267.3, 11.0 Hz),	
(126 MHz, $CDCl_3$)	147.2 (dd, J = 14.6, 3.7 Hz), 133.0 (d, J = 3.7 Hz), 131.0 (d, J = 2.7 Hz), 126.6 (dd, J = 10.5, 2.3 Hz), 125.8 (d, J = 23.8 Hz), 108.2 (dd, J = 34.8, 2.7 Hz), 89.7 (dd, J = 7.8, 3.2 Hz).	
FTIR, cm^{-1}:	2930 (m), 1584 (s), 1429 (s), 1325 (s).	
(thin film)		
HRMS:	Calcd for $(C_9H_3ClF_2IN+H)^+$	325.9040
(ESI)	Found	325.9036
TLC	R_f = 0.39 (UV)	
(9:1 hexanes–ethyl acetate)		

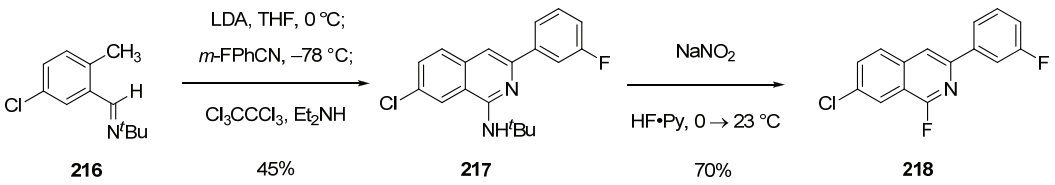


3-Bromo-4-chloro-5-fluoro-7-iodoisoquinoline (**215**)

Bromine (19 μL, 0.372 mmol, 6 equiv) was added to an ice-cooled suspension of 4-chloro-5-fluoro-7-iodoisoquinolin-3-amine (**213**) (20 mg, 0.062 mmol, 1 equiv) in concentrated aqueous hydrobromic acid solution (48 wt %, 1 mL). After 10 min, a solution of sodium nitrite (21 mg, 0.310 mmol, 5 equiv) in water (0.5 mL) was added dropwise over 5 min. After 30 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 60 min, the reaction mixture was partitioned between saturated aqueous sodium carbonate solution (15 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 15 mL). The organic layers were combined and then dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (20:1 hexanes–ethyl acetate), affording 3-bromo-4-chloro-5-fluoro-7-iodoisoquinoline (**215**) as a white solid (19.5 mg, 81%).

Melting Point	165–167 ºC
^{1}H NMR: (500 MHz, $CDCl_3$)	8.82 (d, 1H, J = 2.3 Hz), 8.18 (s, 1H), 7.74 (dd, 1H, J = 11.2, 1.6 Hz).
^{19}F NMR: (470 MHz, $CDCl_3$)	–109.8 (d, J = 11.8 Hz).

^{13}C NMR :	155.7 (d, J = 268.2 Hz), 148.3 (d, J = 1.8 Hz), 139.1,	
(126 MHz, $CDCl_3$)	133.0 (d, J = 5.5 Hz), 131.0, 126.20 (d, J = 25.63 Hz),	
	125.3 (d, J = 3.7 Hz), 124.9 (d, J = 9.2 Hz), 91.5 (d, J =	
	7.3 Hz).	
FTIR, cm^{-1}:	2926 (m), 1553 (s), 1460 (s), 1397 (s), 1298 (s).	
(thin film)		
HRMS:	Calcd for $(C_9H_3BrClFIN+H)^+$	385.8239
(ESI)	Found	385.8230
TLC	R_f = 0.33 (UV)	
(9:1 hexanes–ethyl acetate)		



7-Chloro-1-fluoro-3-(3-fluorophenyl)isoquinoline (**218**)

A solution of *n*-butyllithium in hexanes (2.32 M, 226 μL, 0.525 mmol, 1.05 equiv) was added dropwise to an ice-cooled solution of diisopropylamine (78 μL, 0.550 mmol, 1.1 equiv) in tetrahydrofuran (1.0 mL). After 15 min, a solution of imine **216** (105 mg, 0.500 mmol, 1 equiv) in tetrahydrofuran (0.5 mL) was added by cannula, forming a deep purple solution. After 60 min, the reaction flask was cooled to –78 ºC, and 3-fluorobenzonitrile (67 μL, 0.625 mmol, 1.25 equiv) was added, forming a dark brown solution. After 5 min, the dark brown solution was transferred by cannula to a suspension of hexachloroethane (473 mg, 2.00 mmol, 4 equiv) and diethylamine (207 μL, 2.00 mmol, 4 equiv) in tetrahydrofuran (0.5 mL) at –78 ºC. After 30 min, the cooling bath was removed and the reaction flask was allowed to warm to 23 ºC. After 30 min, the reaction mixture was partitioned between saturated aqueous sodium bicarbonate solution (20 mL) and dichloromethane (30 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash-column chromatography (50:1 hexanes–ethyl acetate), affording *N*-*tert*-butyl-7-chloro-3-(3-fluorophenyl) isoquinolin-1-amine (**217**) as a pale yellow oil (75 mg, 45%).

A solution of sodium nitrite (79 mg, 1.14 mmol, 5 equiv) in water (1 mL) was added dropwise to an ice-cooled suspension of *N*-*tert*-butyl-7-chloro-3-(3-fluorophenyl) isoquinolin-1-amine (**217**) (75 mg, 0.228 mmol, 1 equiv) in hydrogen fluoride pyridine

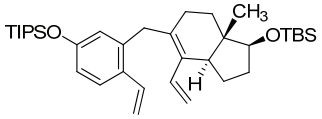
(70% HF, 2 mL) in a Teflon reaction vessel over 5 min. After 30 min, the cooling bath was removed and the reaction vessel was allowed to warm to 23 ºC. After 60 min, saturated aqueous sodium carbonate solution (20 mL) was added slowly (CAUTION: gas evolution). The reaction mixture was then partitioned between saturated aqueous sodium chloride (15 mL) and dichloromethane (20 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The organic layers were combined. The combined solution was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by recrystallization from hexanes, furnishing 7-chloro-1-fluoro-3-(3-fluorophenyl) isoquinoline (**218**) as a pale yellow solid (44 mg, 70%).

Melting Point	118–119 ºC
^{1}H NMR: (500 MHz, $CDCl_3$)	8.10 (d, 1H, *J* = 8.7 Hz), 7.89 (s, 1H), 7.85 (d, 1H, *J* = 8.2 Hz), 7.84 (s, 1H), 7.80 (app dt, 1H, *J* = 10.5, 2.1 Hz), 7.58 (dd, 1H, *J* = 8.7, 1.8 Hz), 7.45 (app td, 1H, *J* = 8.0, 6.0 Hz), 7.12 (app td, 1H, *J* = 8.2, 2.7 Hz).
^{19}F NMR: (470 MHz, $CDCl_3$)	–69.7 (s), –113.0 (ddd, *J* = 10.3, 8.0, 5.7 Hz).
^{13}C NMR :	163.3 (d, *J* = 246.3 Hz), 159.5 (d, *J* = 243.5 Hz), 148.3

(126 MHz, $CDCl_3$)	(d, J = 17.4 Hz), 141.2 (d, J = 5.5 Hz), 139.8 (d, J = 7.3 Hz), 138.4, 130.3 (d, J = 8.2 Hz), 129.0, 125.8 (d, J = 3.7 Hz), 125.0, 122.3 (d, J = 2.7 Hz), 116.2 (d, J = 22.0 Hz), 115.1 (d, J = 33.9 Hz), 114.0 (d, J = 5.5 Hz), 113.9 (d, J = 22.9 Hz).	
FTIR, cm^{-1}:	2980 (m), 2970 (m), 1738 (s), 1379 (vs), 1314 (m).	
(thin film)		
HRMS:	Calcd for $(C_{15}H_8ClF_2N+H)^+$	276.0386
(ESI)	Found	276.0378
TLC	R_f = 0.32 (UV)	
(20:1 hexanes–ethyl acetate)		

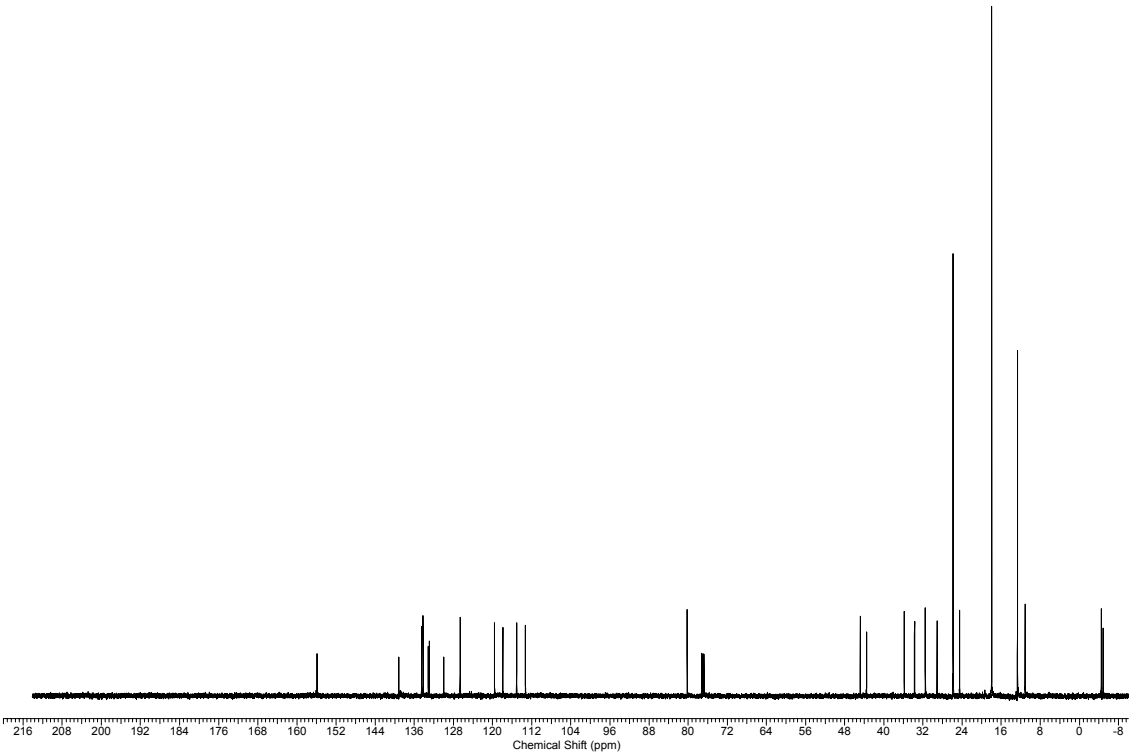
Appendix A

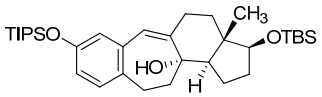
Catalog of Spectra


TIPSO
CH3
OTBS
H

115

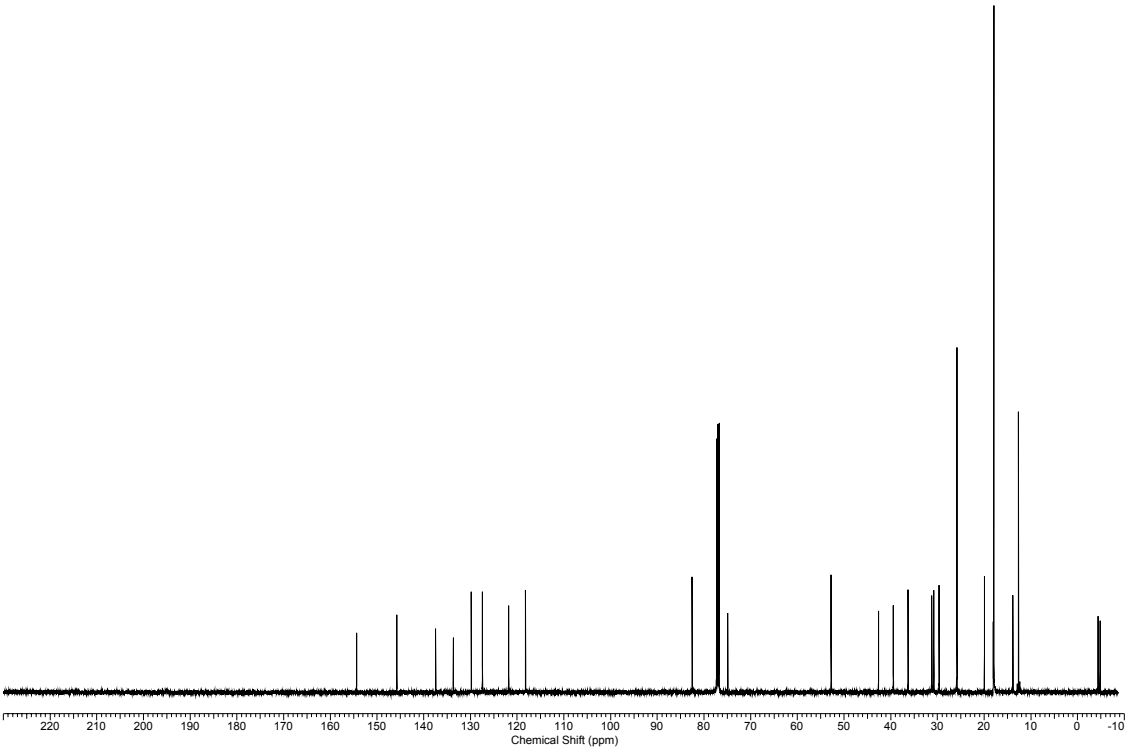
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


216 208 200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0 -8
Chemical Shift (ppm)


TIPSO
CH3
OTBS
HO
H

123

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)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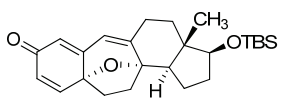
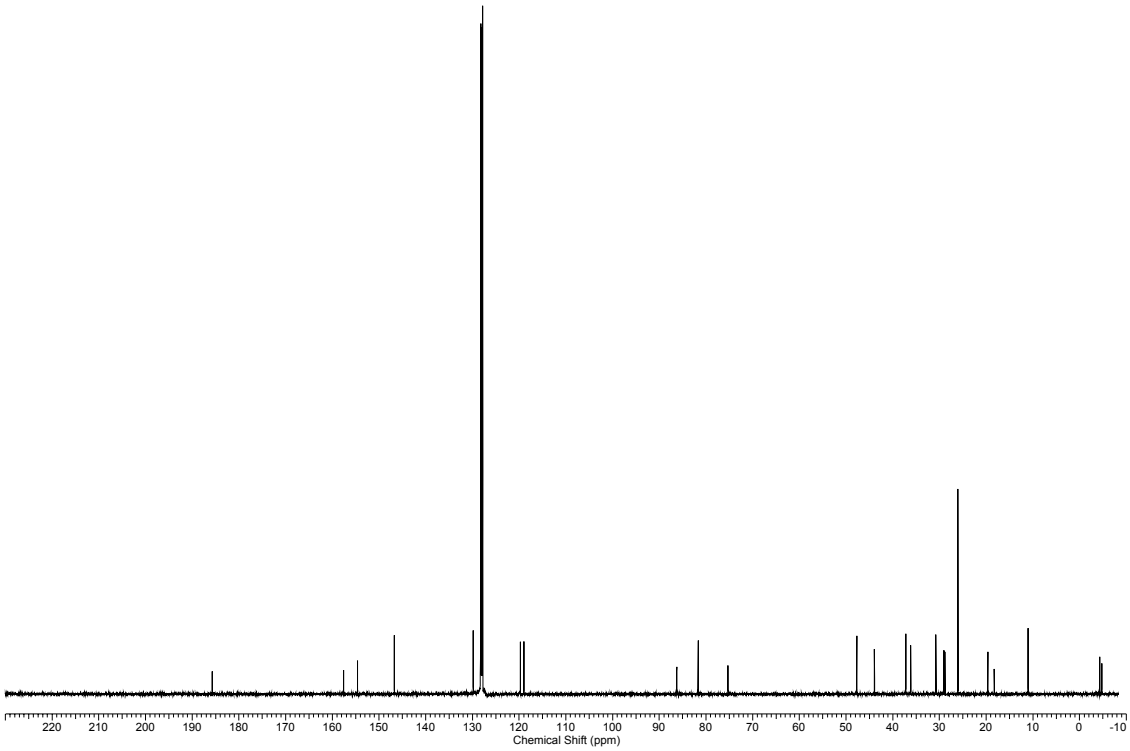
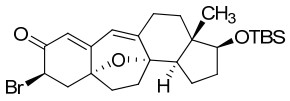
Chemical Shift (ppm)


CH3
OTBS
O
O
H

74

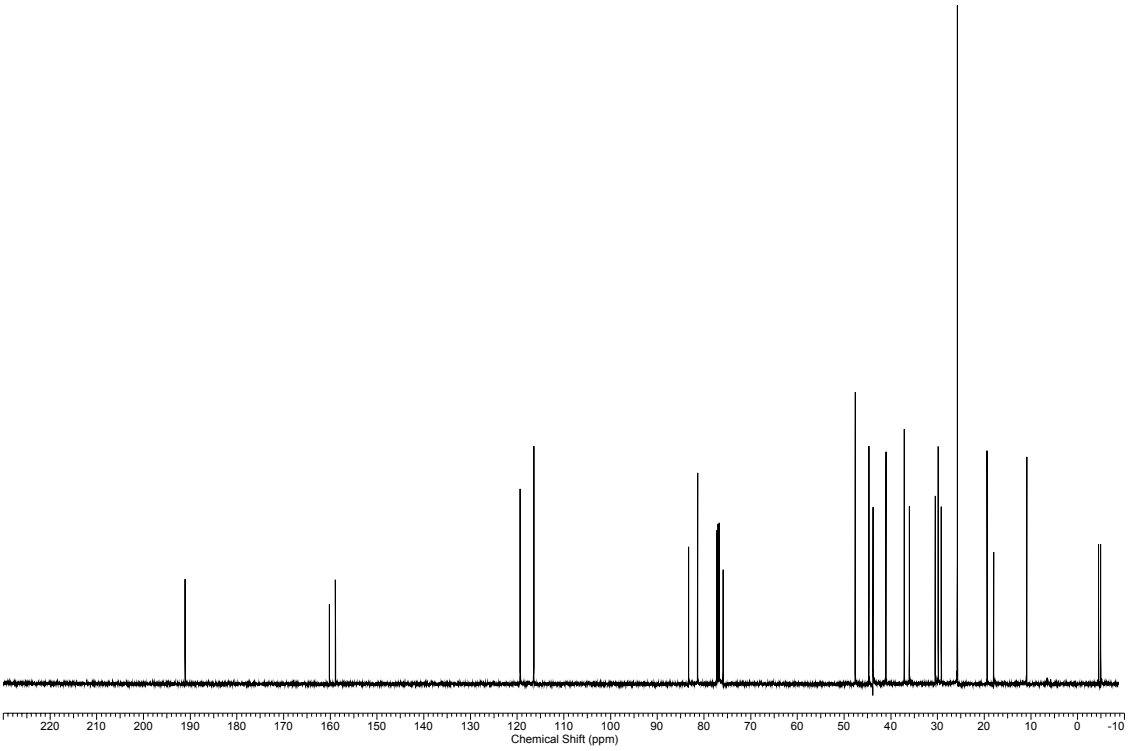
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

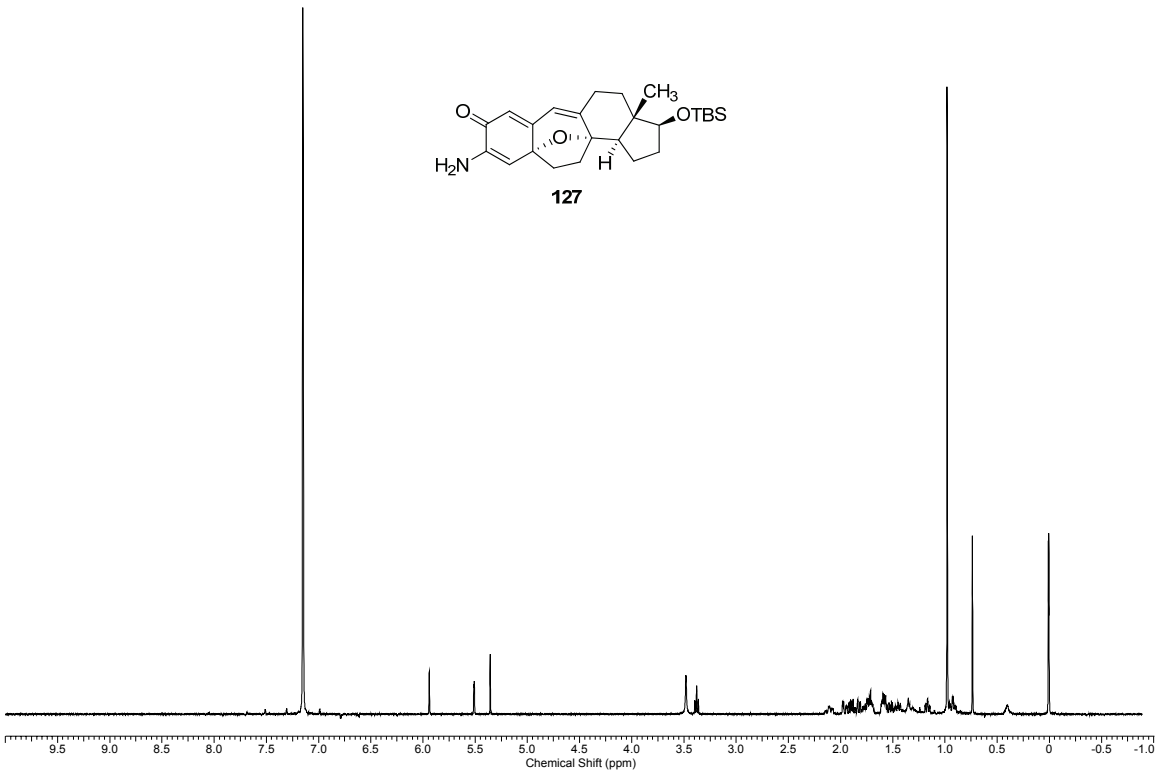

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

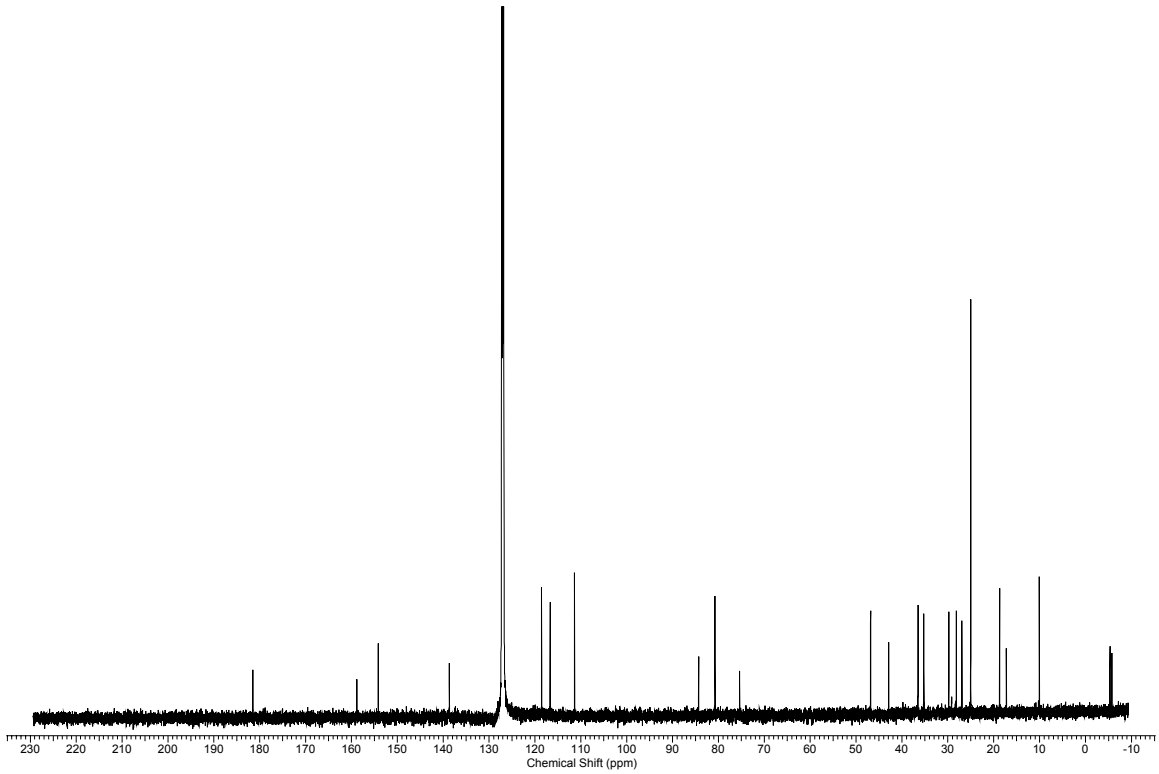

O
CH3
OTBS
O
Br
H

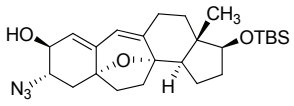
125

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

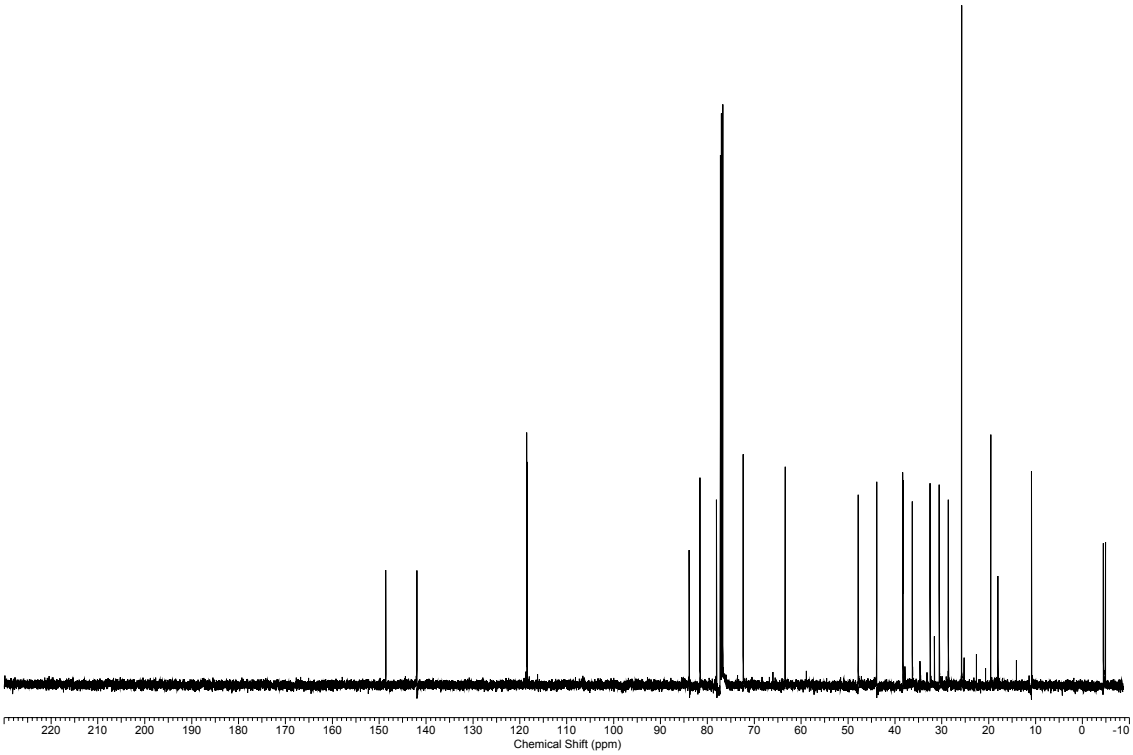

CH3
OTBS
O
O
H2N
H
127
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5 -1.0
Chemical Shift (ppm)

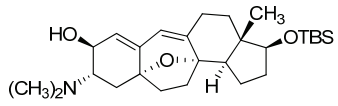

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


HO
CH3
OTBS
O
N3
H

112

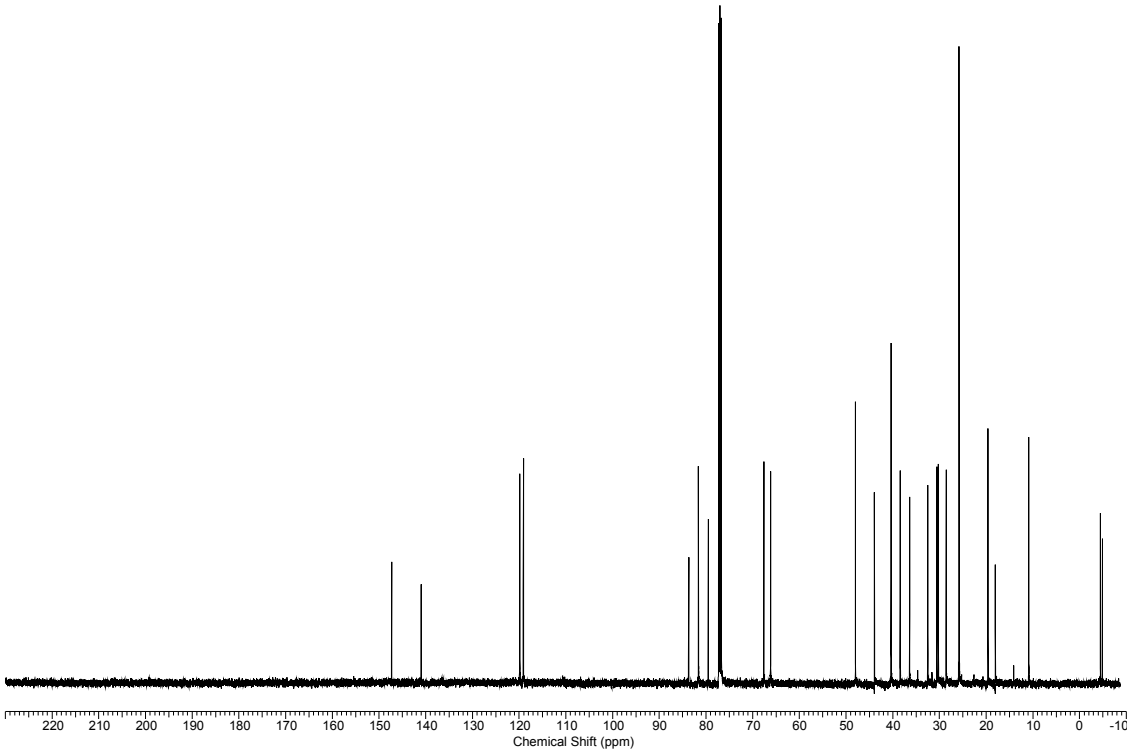
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

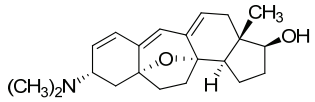

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


HO
CH3
OTBS
O
(CH3)2N
H

133

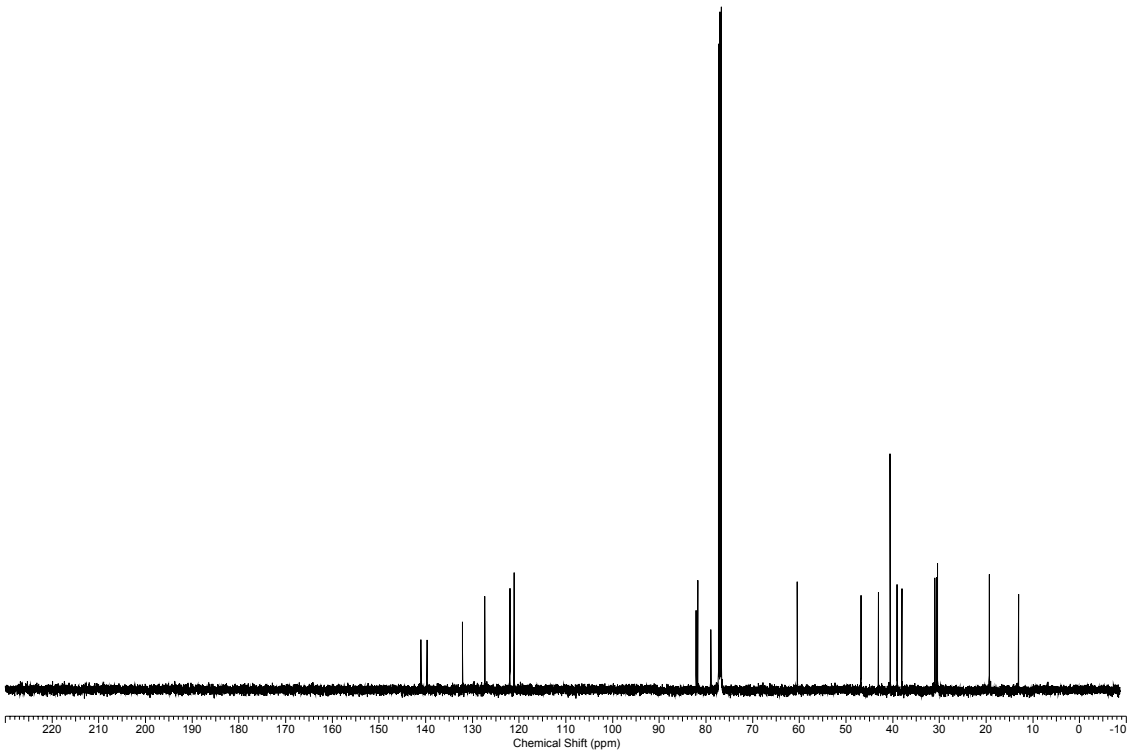
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

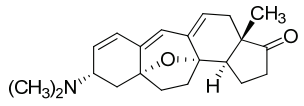

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


CH3
OH
O
(CH3)2N
H

134

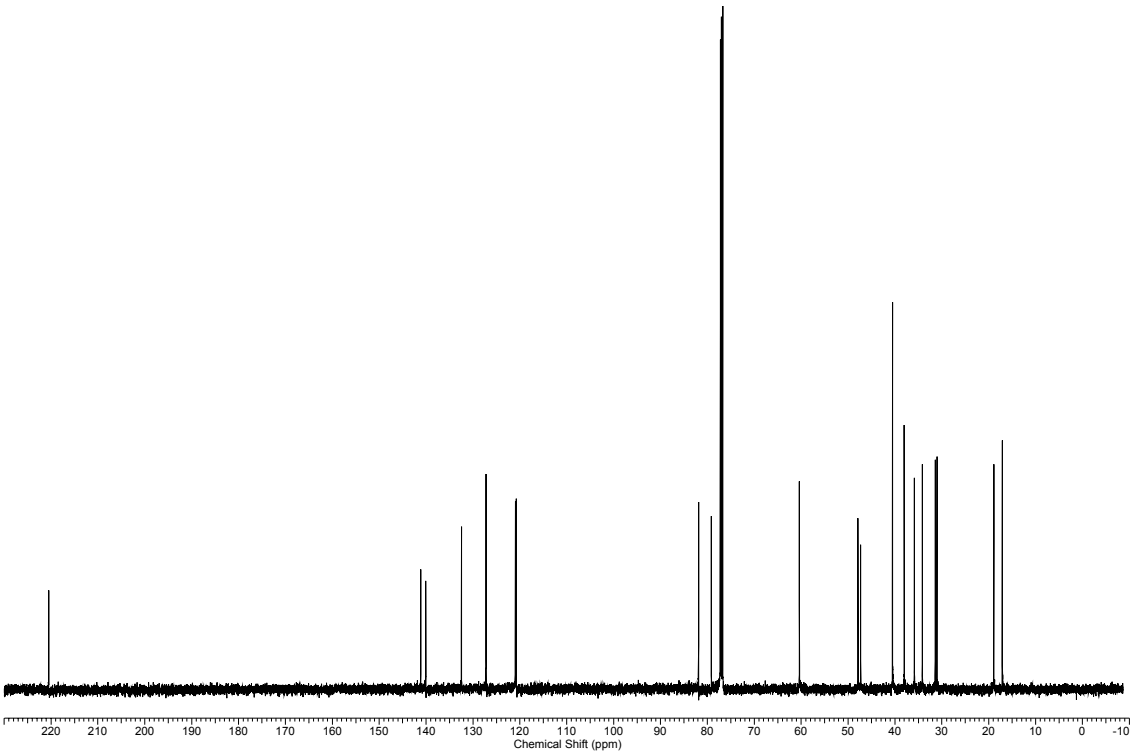
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

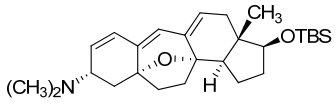

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


CH3
O
O
H
(CH3)2N

109

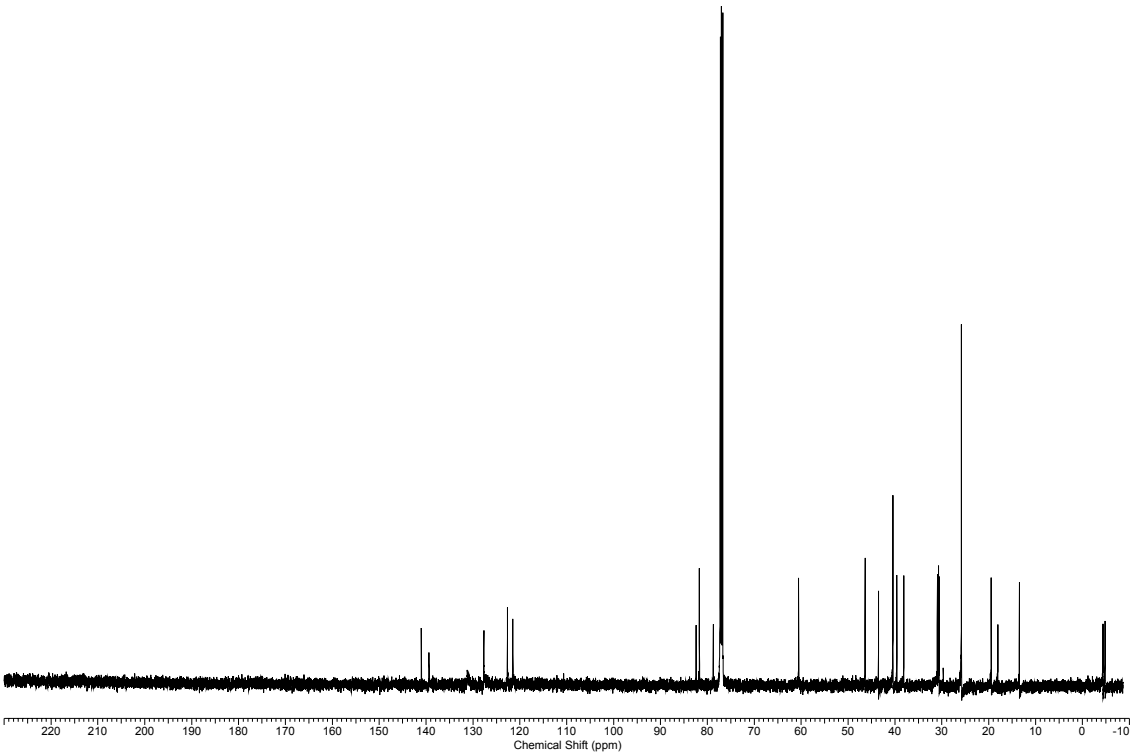
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

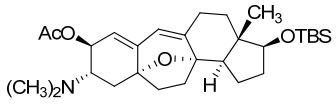

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


CH3
OTBS
O
(CH3)2N
H

135

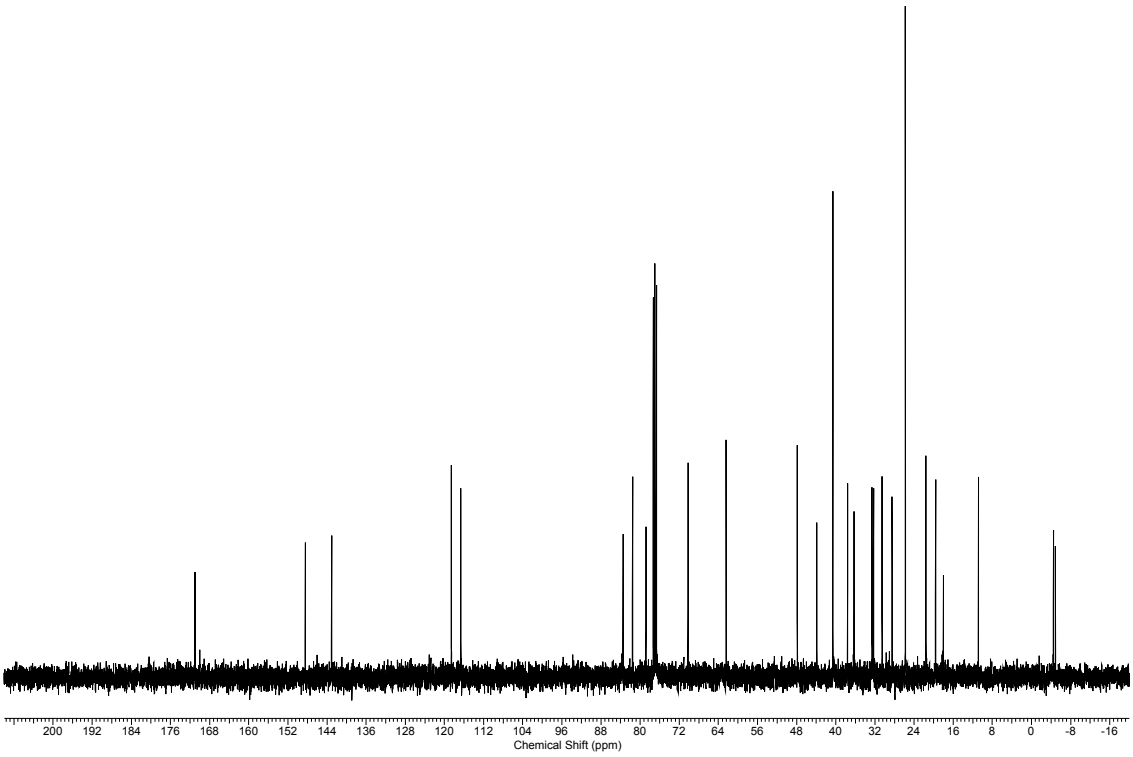
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

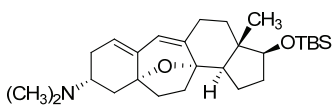

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


AcO
CH3
OTBS
O
(CH3)2N
H

137

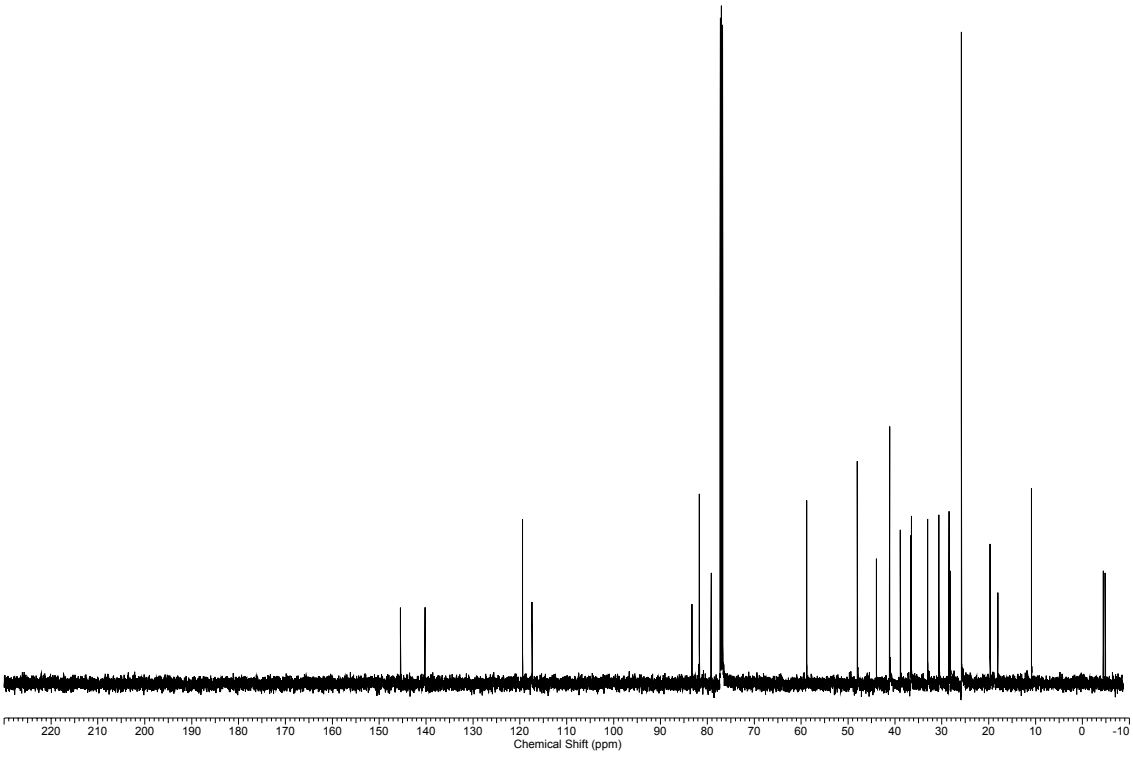
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

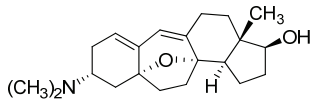

200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0 -8 -16
Chemical Shift (ppm)


CH3
OTBS
O
(CH3)2N
H

139

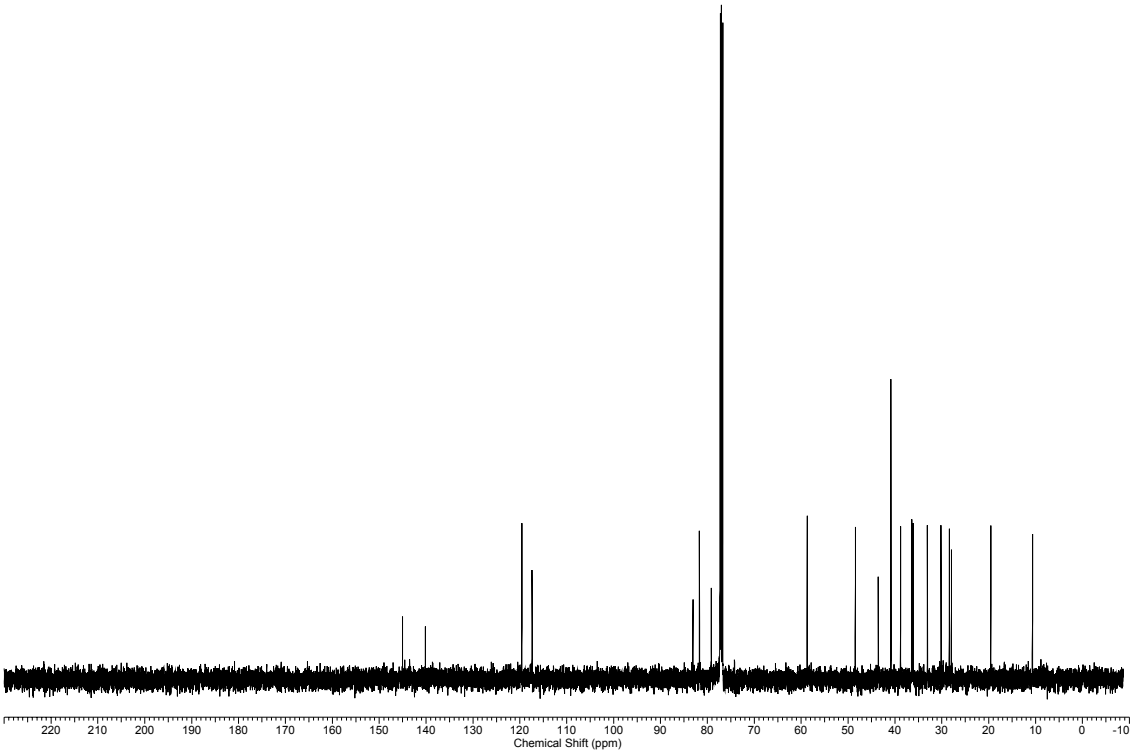
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5
Chemical Shift (ppm)

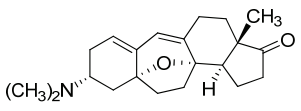

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


CH3
OH
O
(CH3)2N
H

154

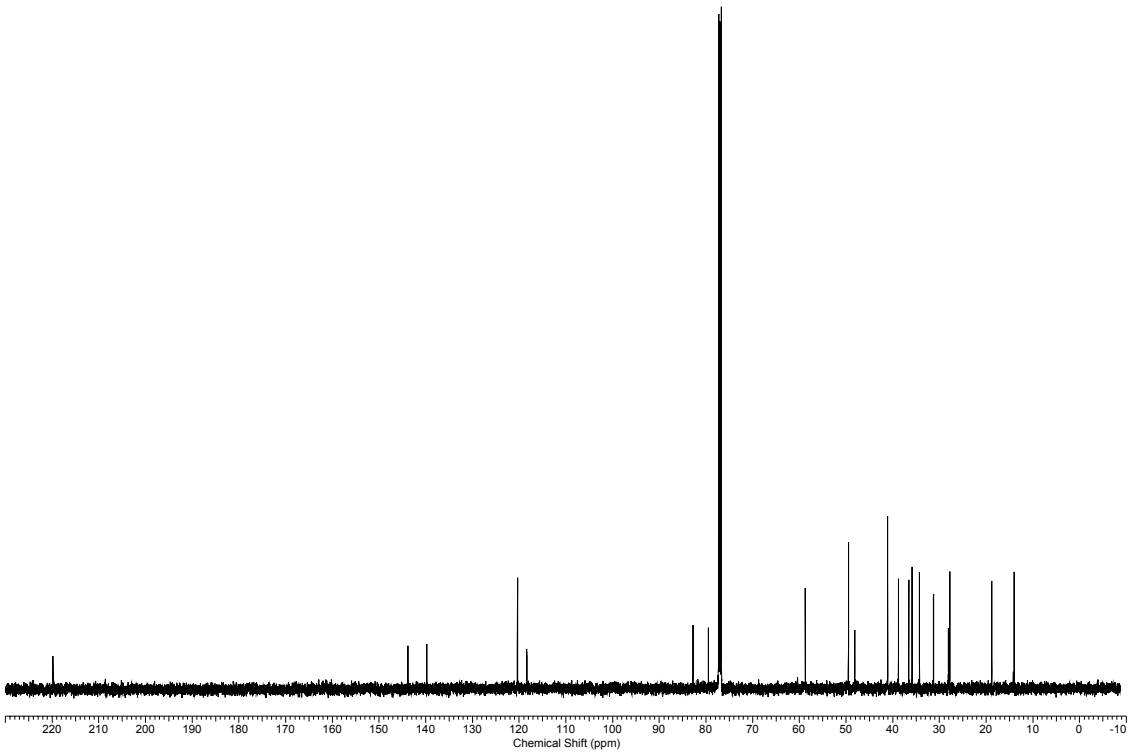
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

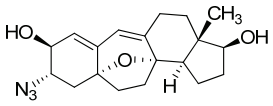

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


CH3
O
O
H
(CH3)2N

110

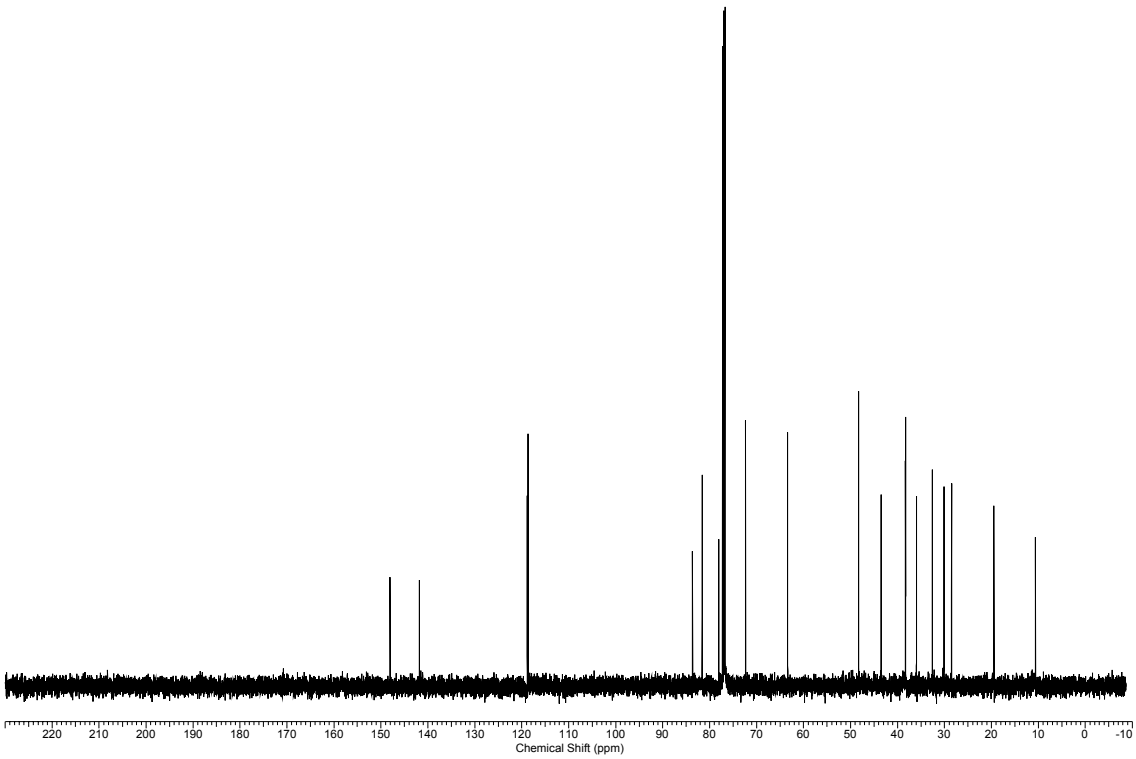
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

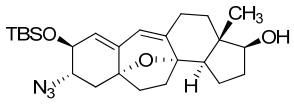

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


HO
CH3
OH
O
N3
H

155

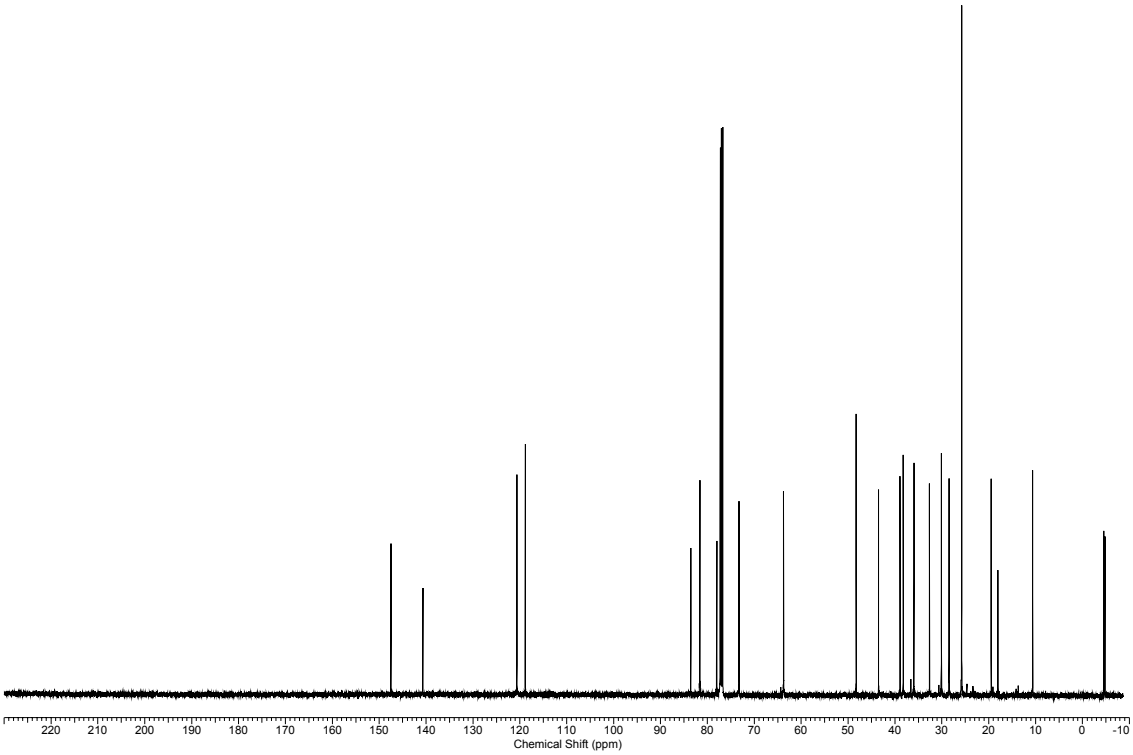
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

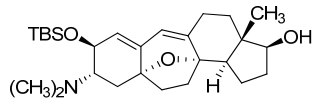

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


TBSO
CH3
OH
O
N3
H

140

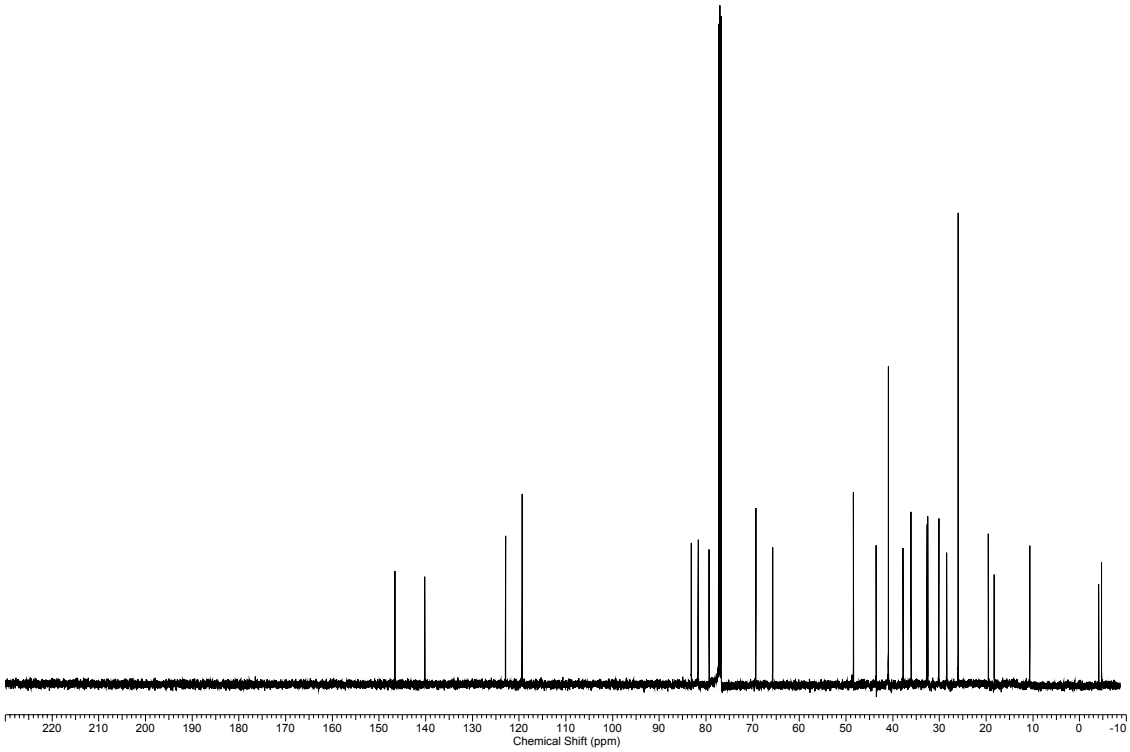
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5
Chemical Shift (ppm)

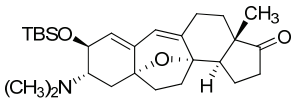

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


TBSO
CH3
OH
O
(CH3)2N
H

143

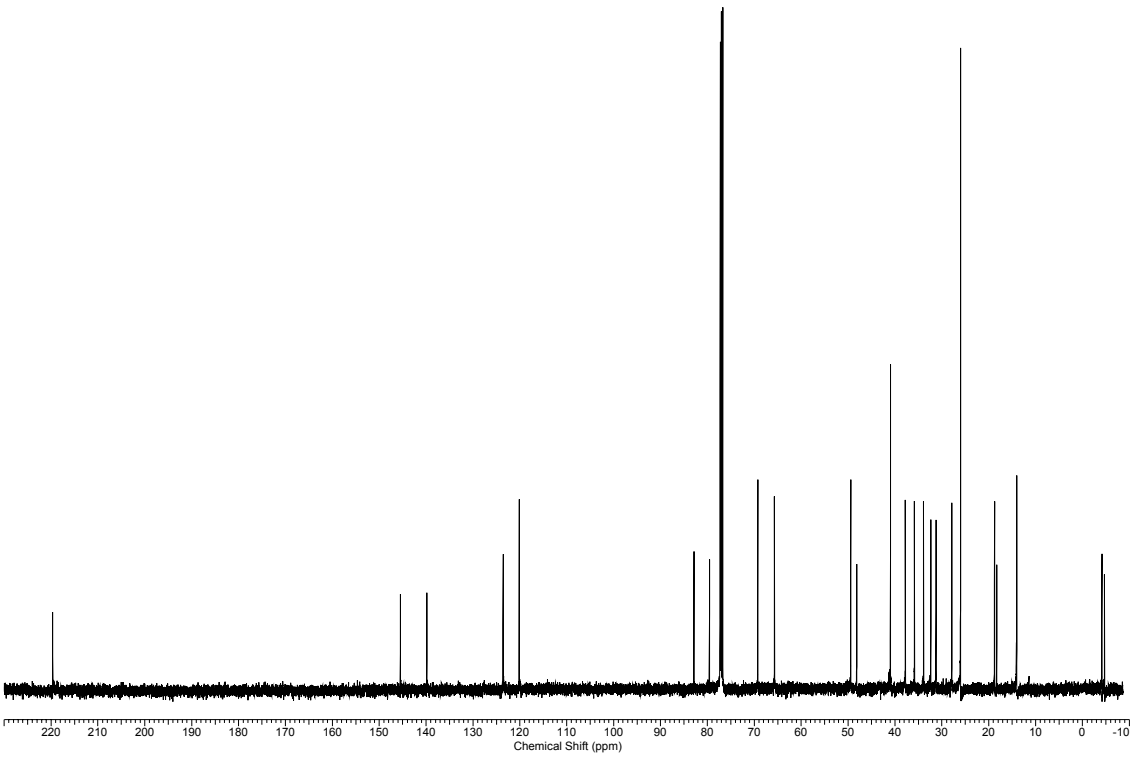
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

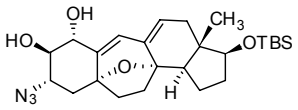

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


TBSO
CH3
O
O
H
(CH3)2N

111

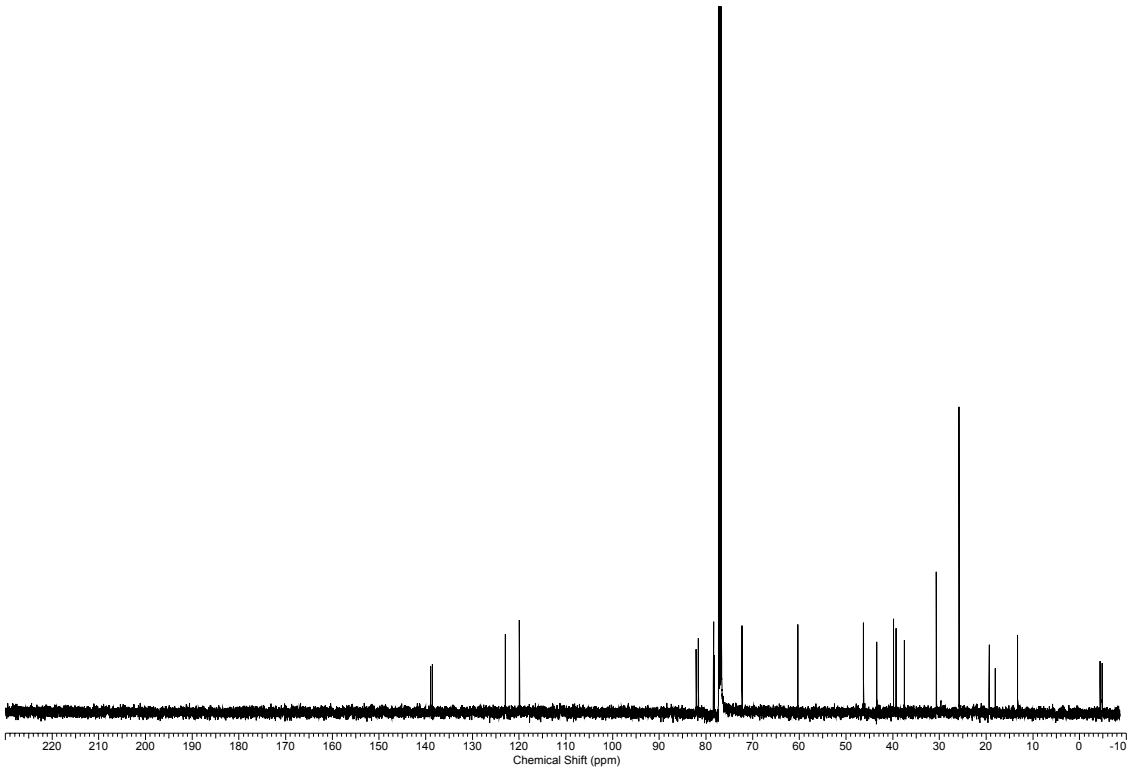
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

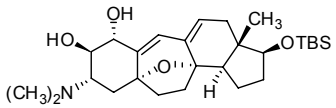

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


OH
HO
CH3
OTBS
O
N3
H

147

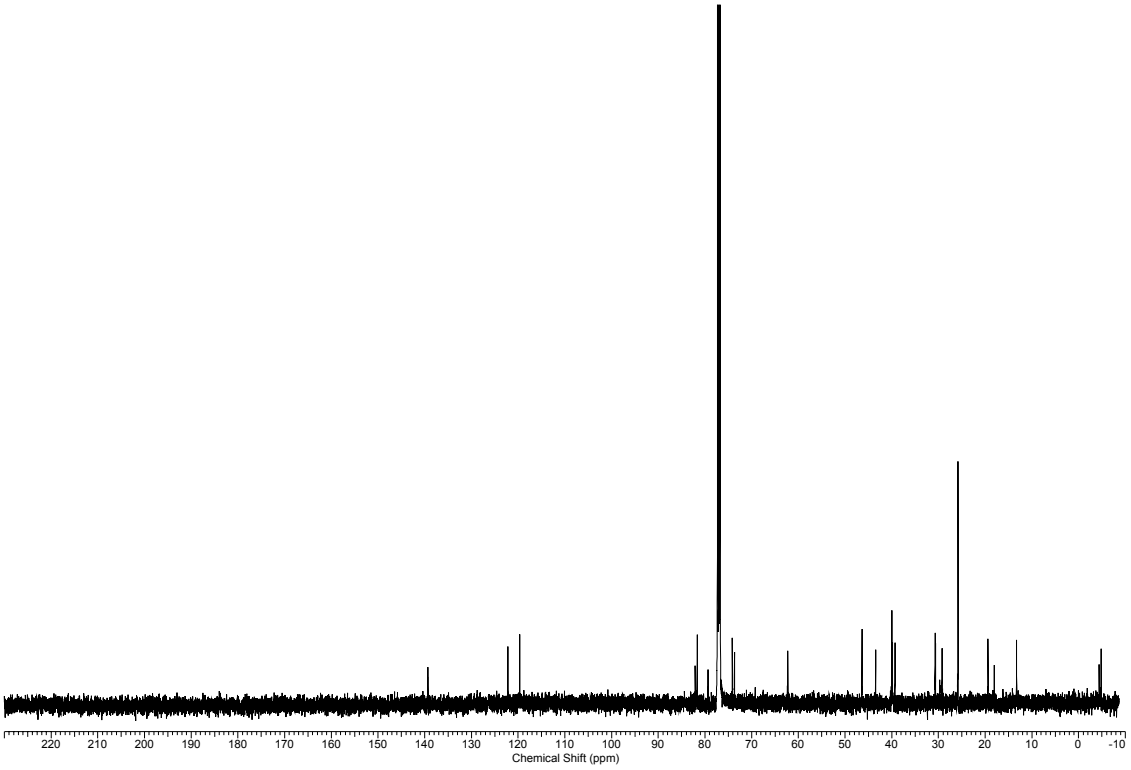
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

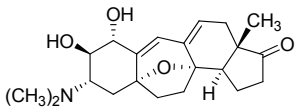

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


OH
HO
CH3
OTBS
O
(CH3)2N
H

148

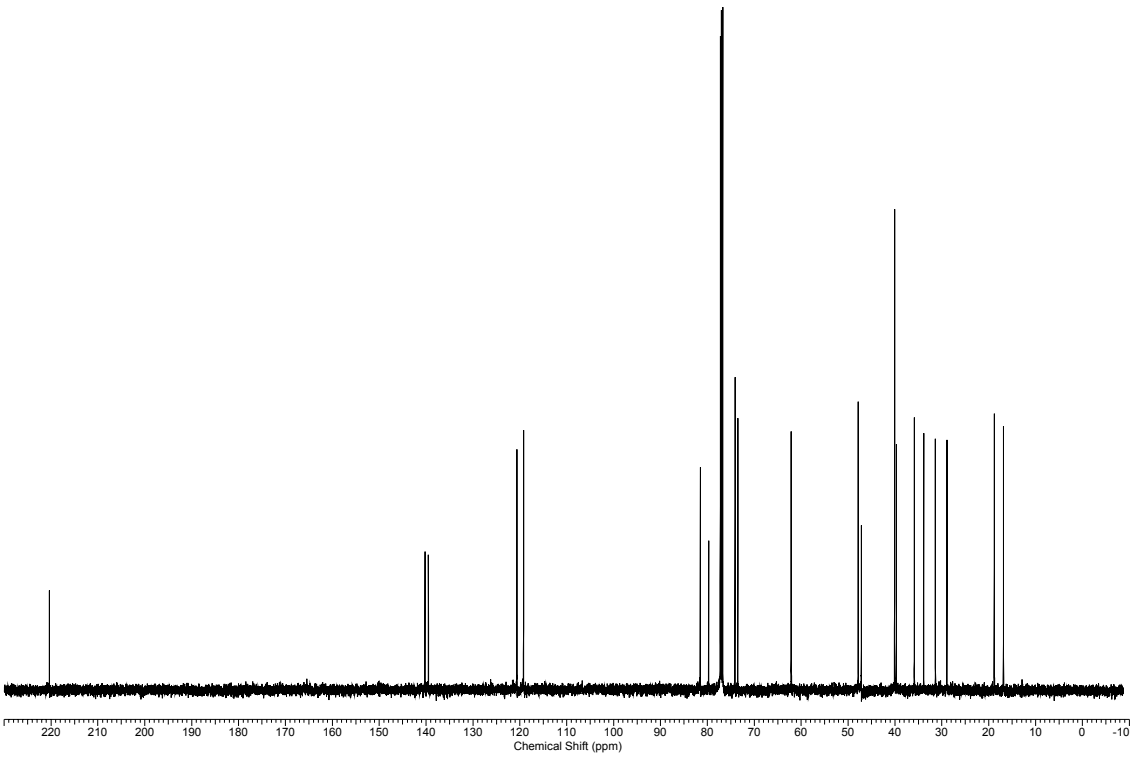
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

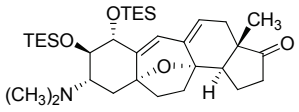

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


OH
HO
CH3
O
O
H
(CH3)2N

23

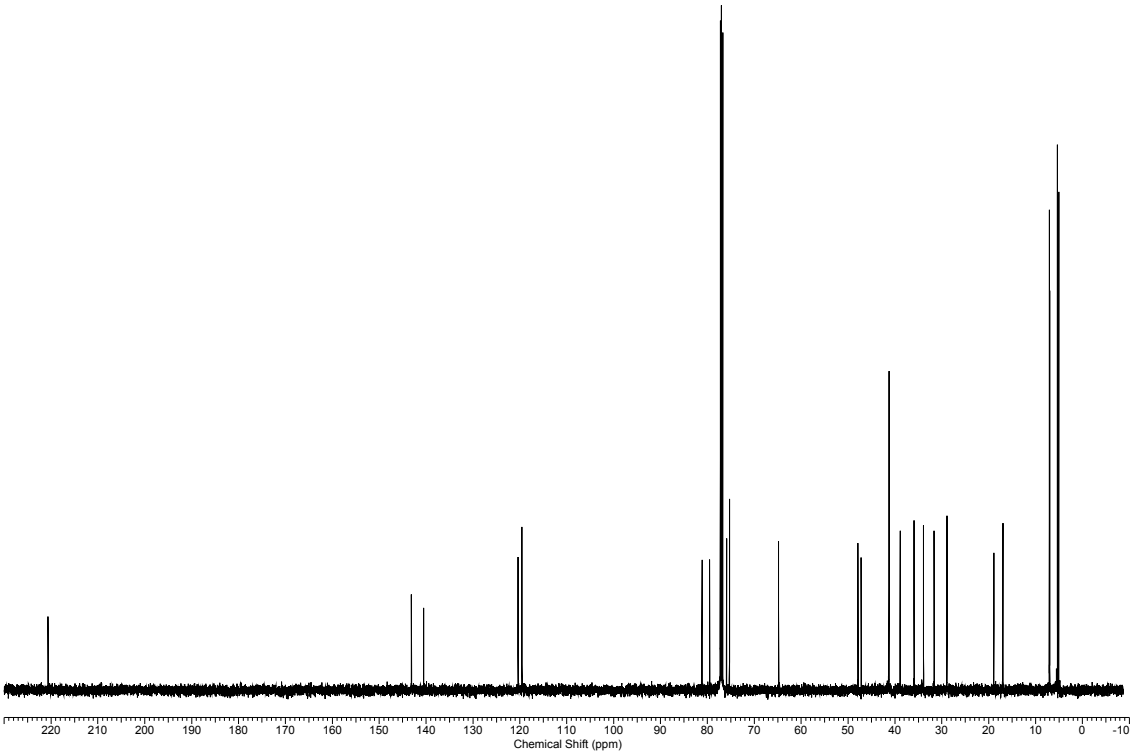
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

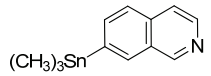

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


OTES
TESO
$(CH_3)_2N$
O
H
CH_3
O

108

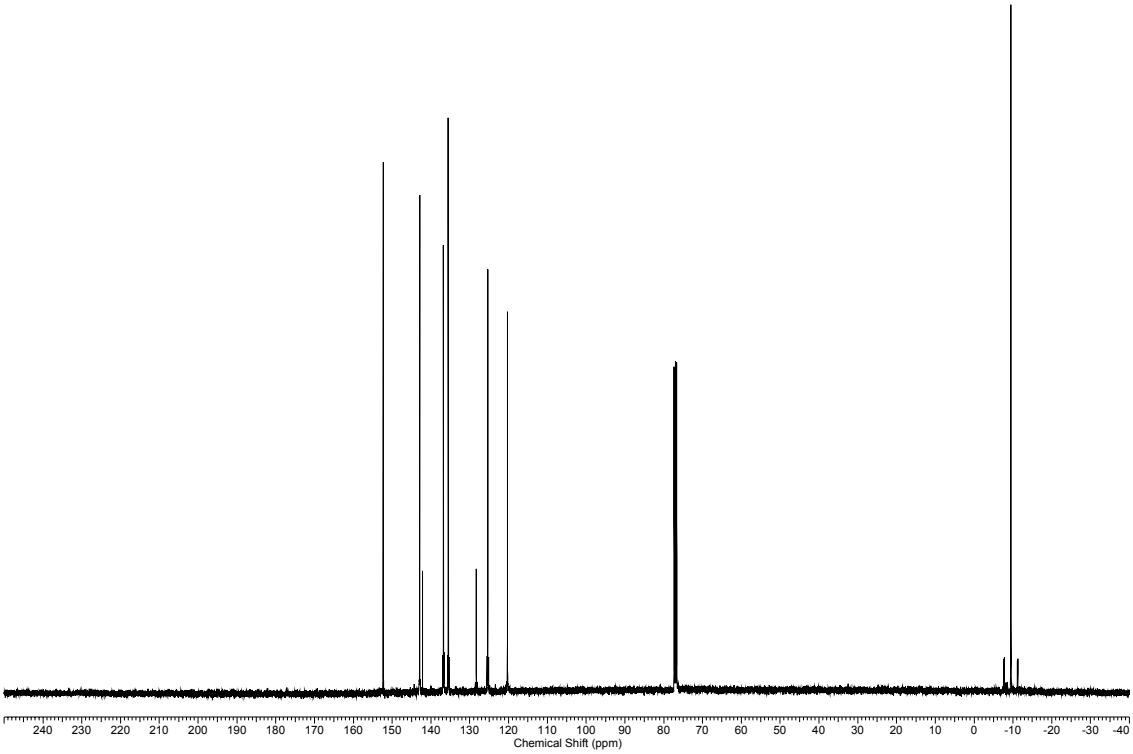
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

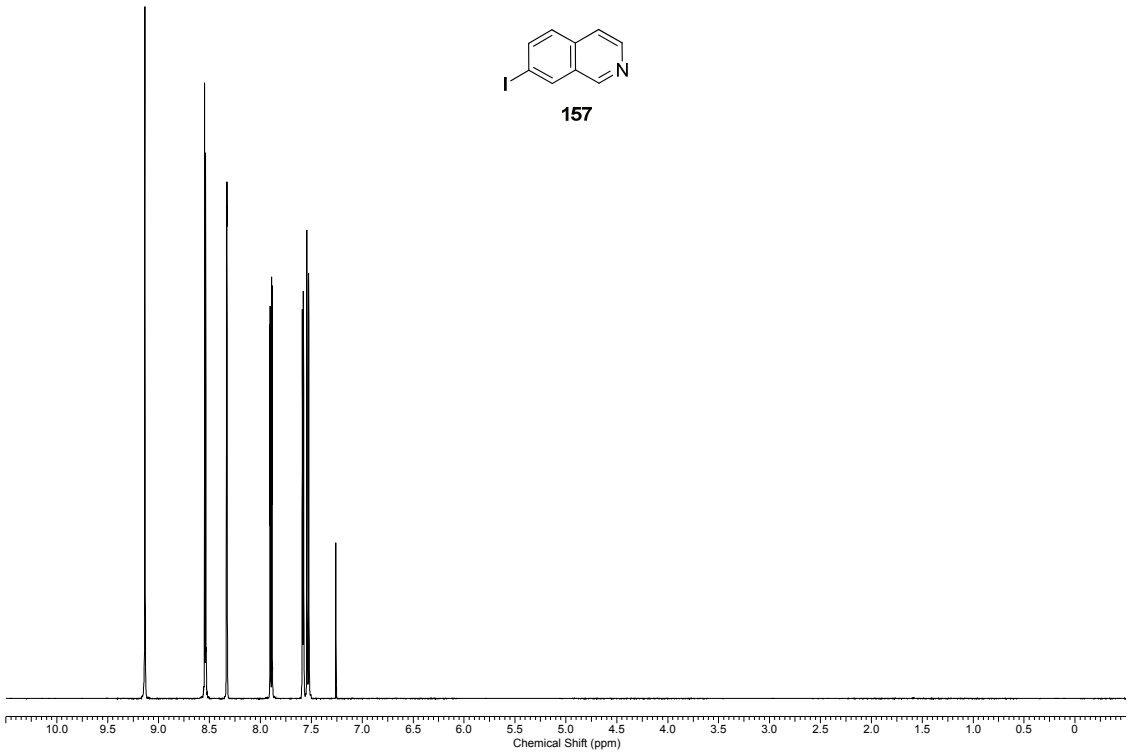

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

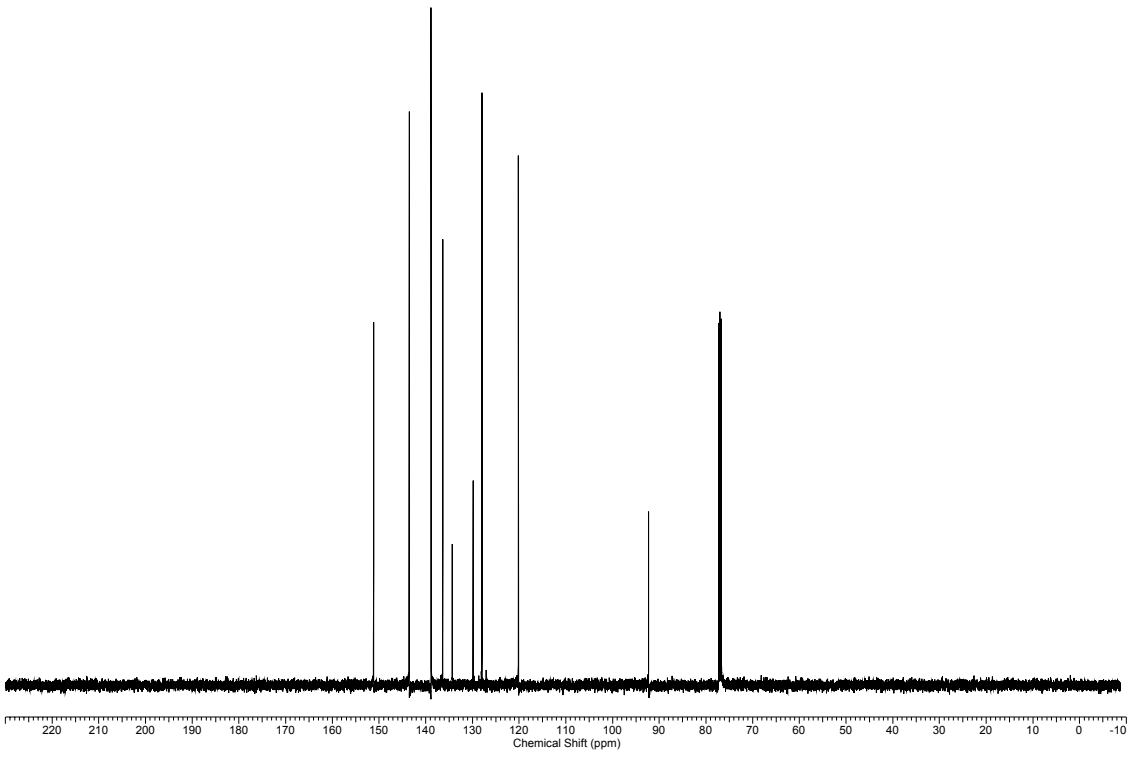

(CH3)3Sn
N

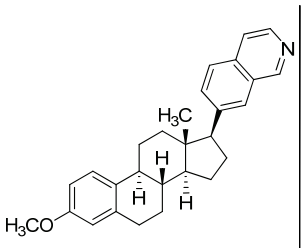
188

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

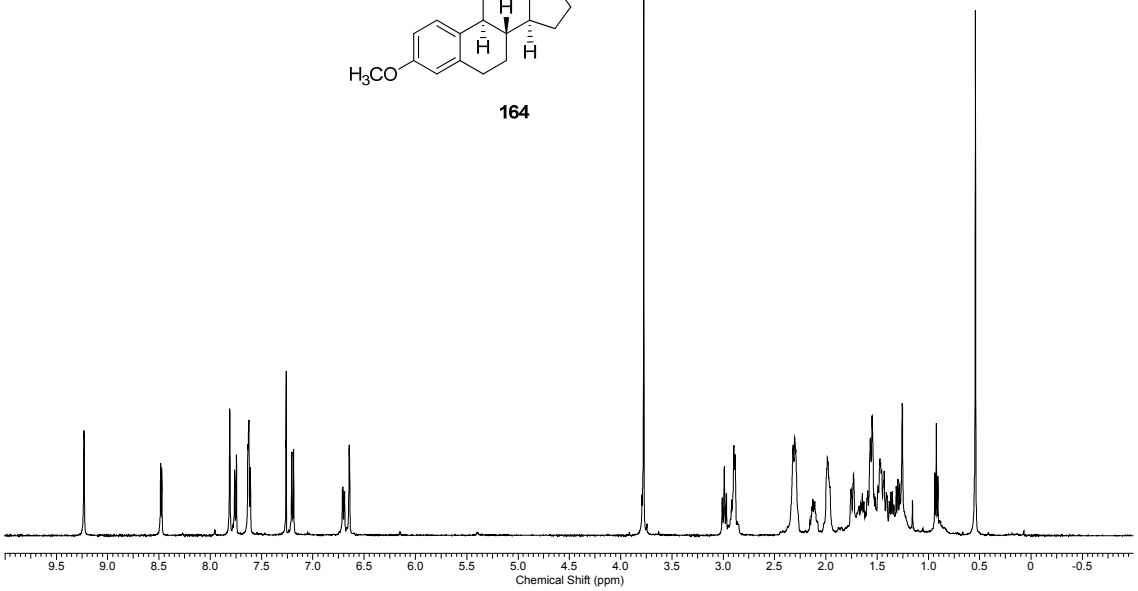

240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
Chemical Shift (ppm)

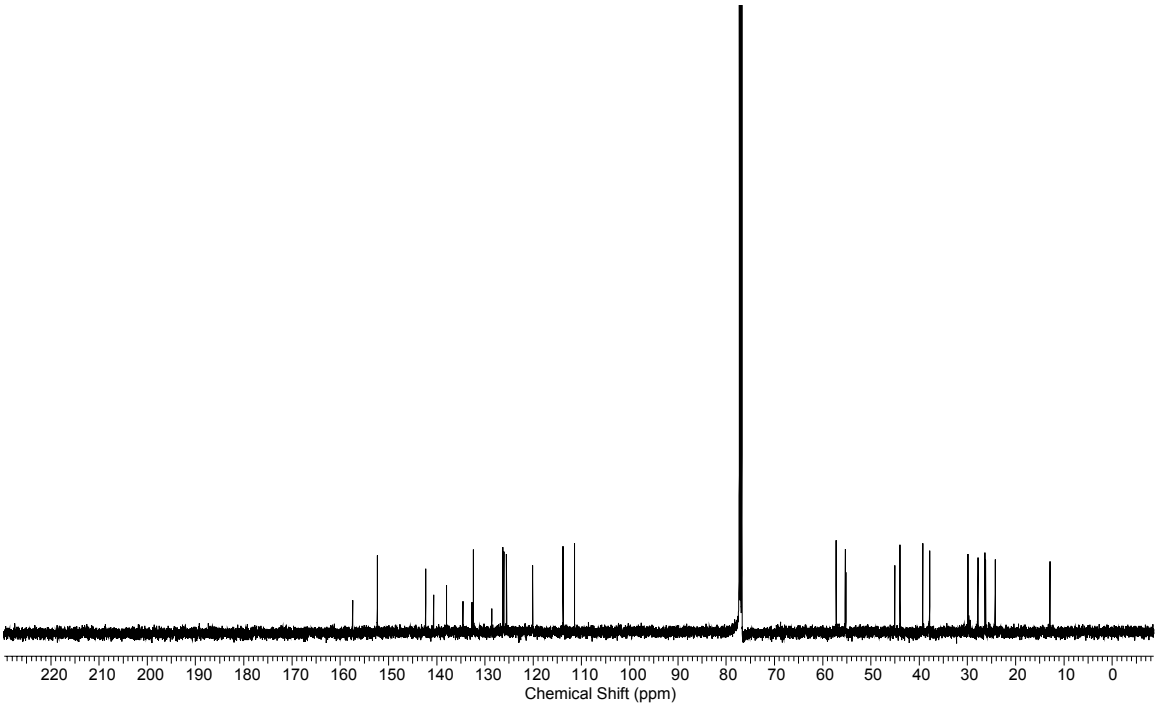

I
N
157
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

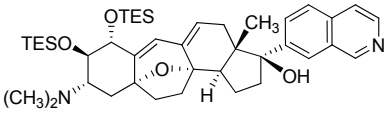

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


N
H3C
H
H
H
H3CO

164

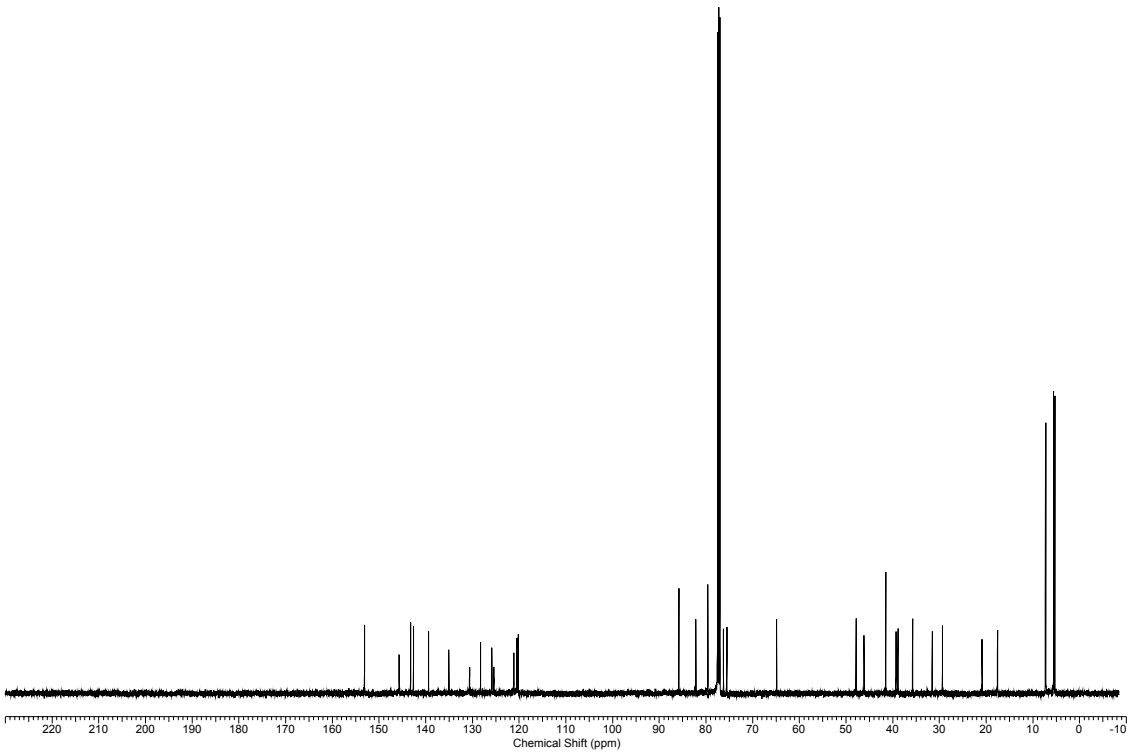

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5
Chemical Shift (ppm)

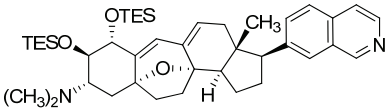

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)


OTES
TESO
$(CH_3)_2N$
O
H
CH_3
N
OH

159

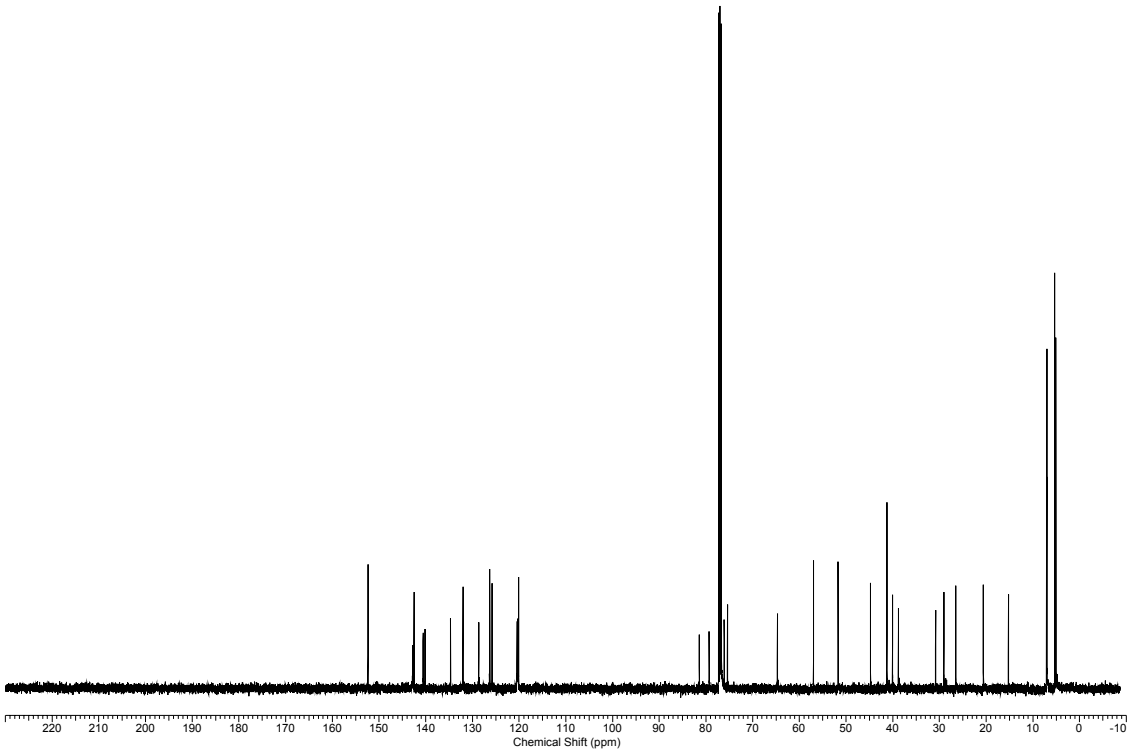
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

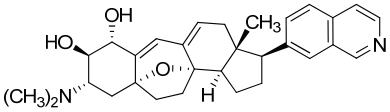

OTES
TESO
$(CH_3)_2N$
O
H
CH_3
N

170

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

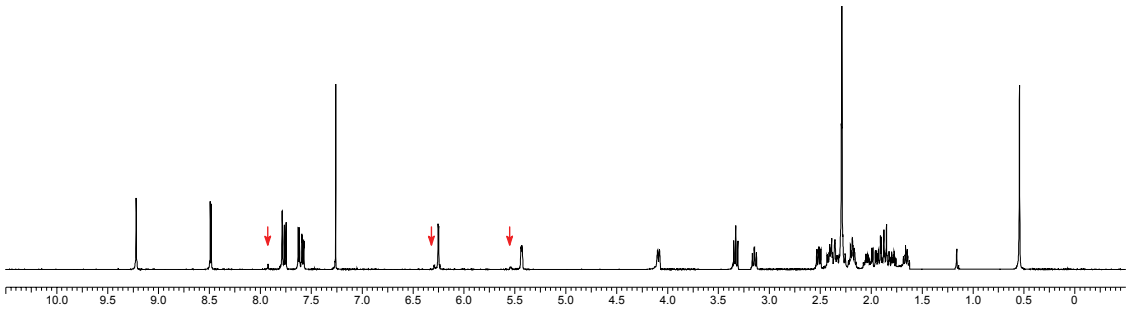
Purification of Cortistatin A (**1**).



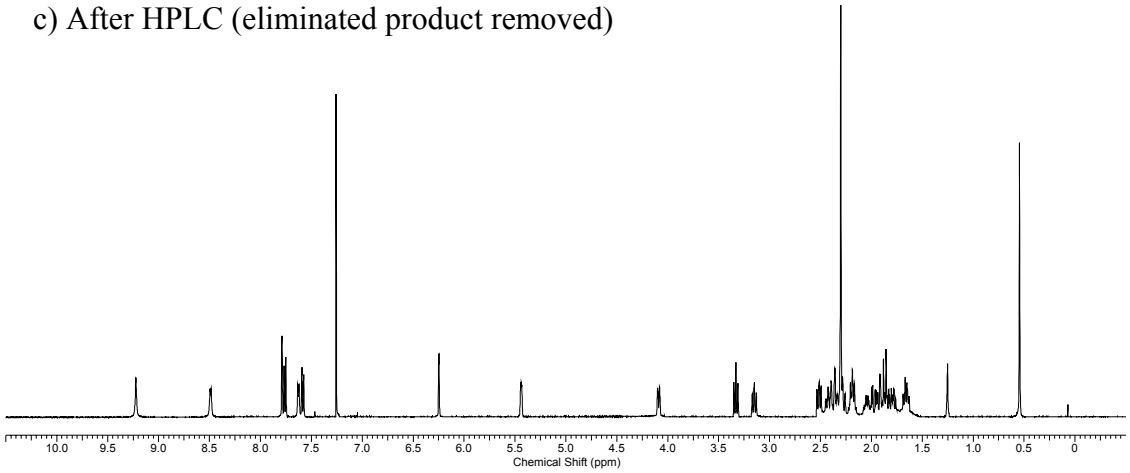
1

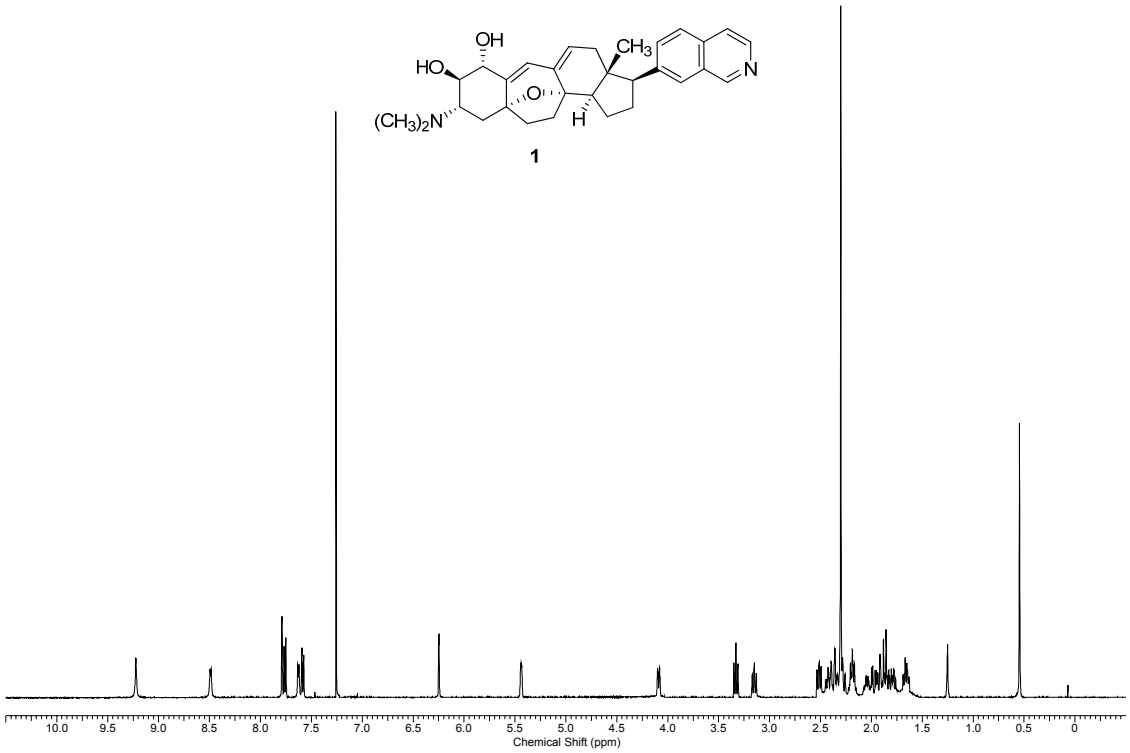
a) After Davisil® column

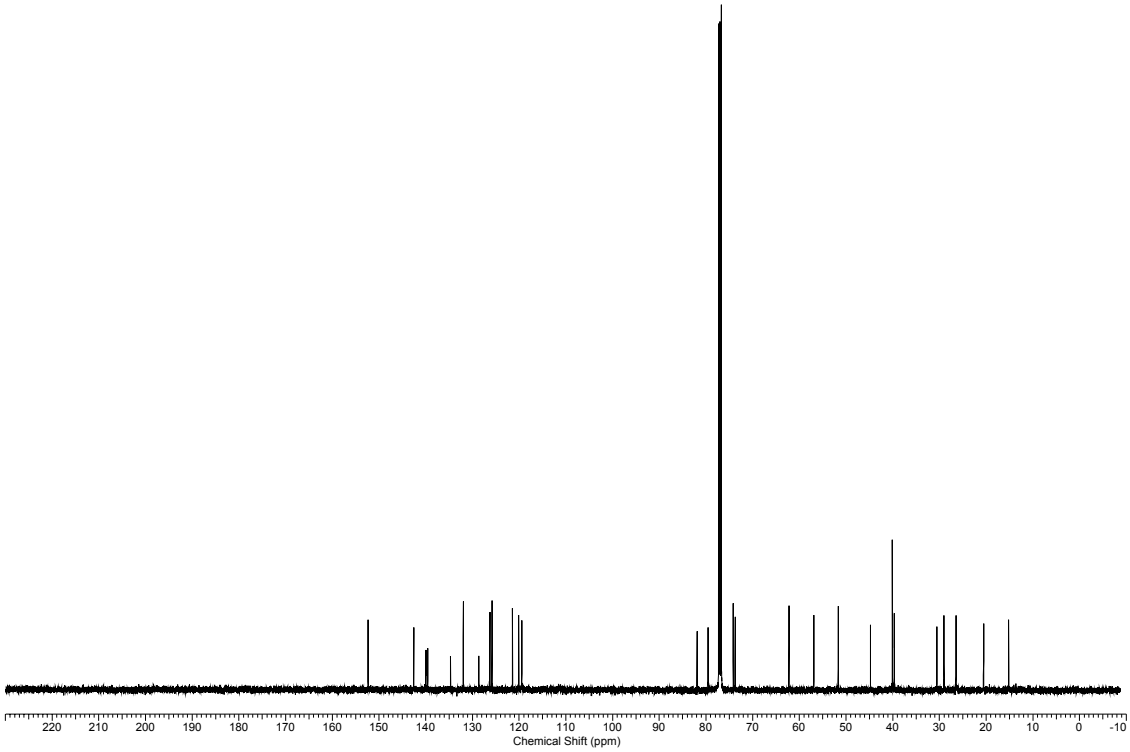
b) After LH-20 column (tetra-*n*-butylammonium salts

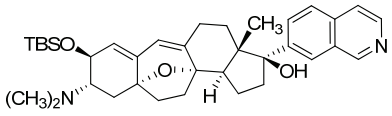


c) After HPLC (eliminated product removed)



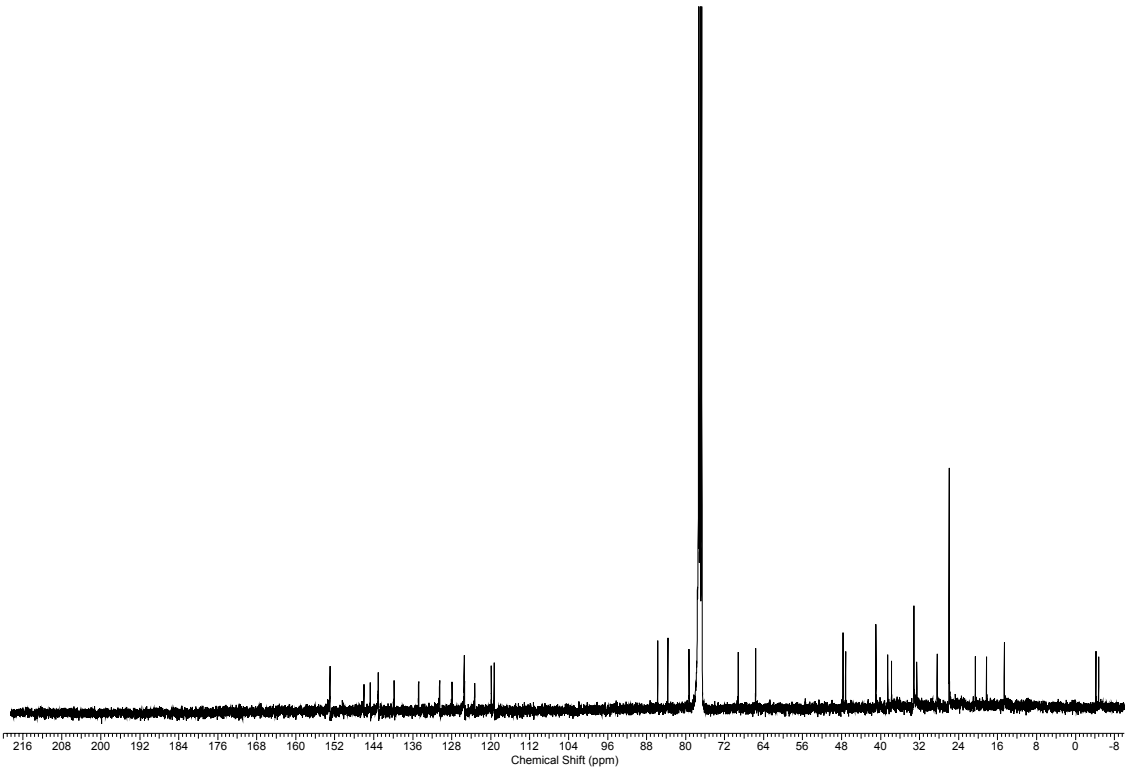

OH
HO
CH3
N
O
(CH3)2N
H
1
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

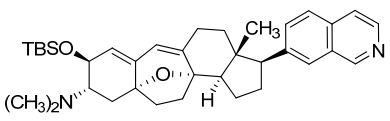

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


TBSO
$(CH_3)_2N$
O
H
CH_3
OH
N

160

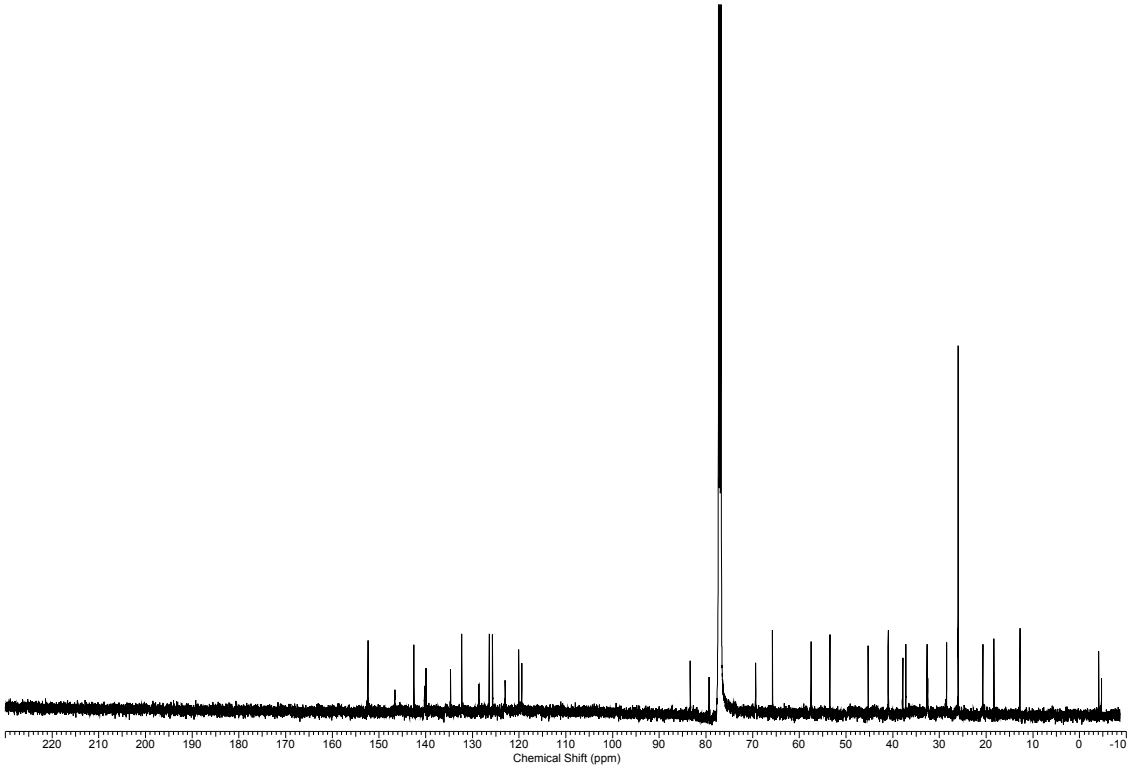
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


216 208 200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0 -8
Chemical Shift (ppm)

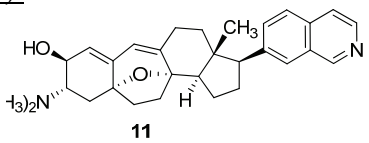

TBSO
$(CH_3)_2N$
O
H
CH_3
N

189

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

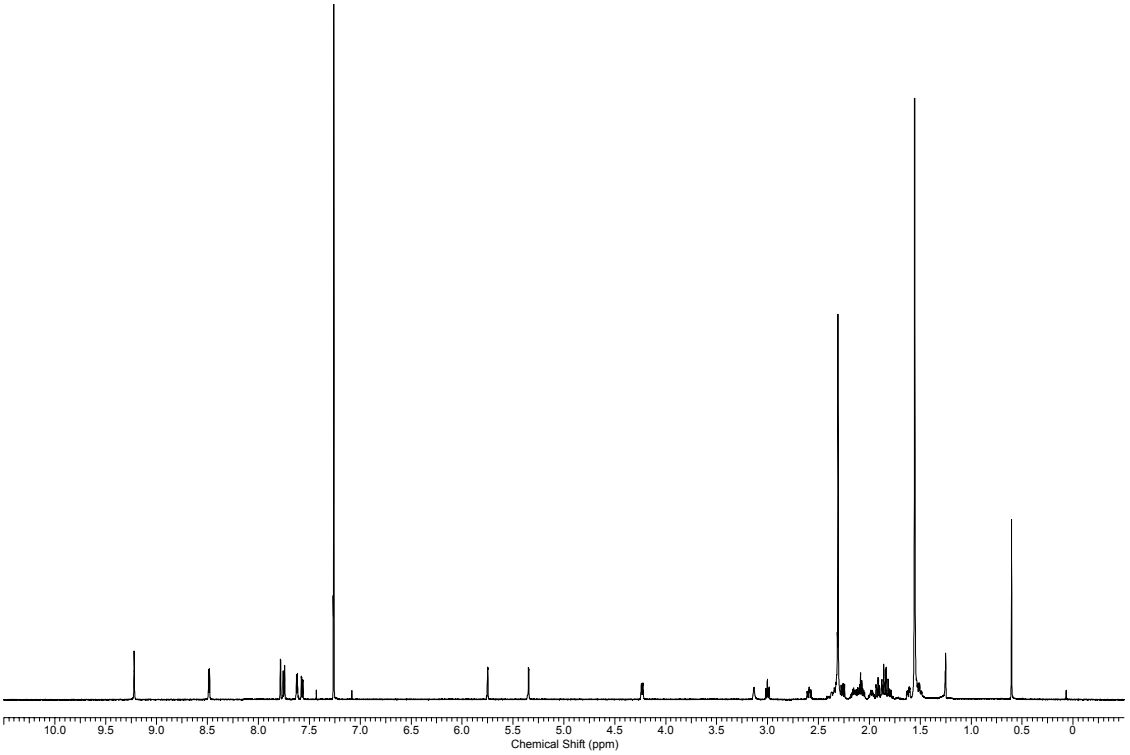
Purification of Cortistatin L (**11**).

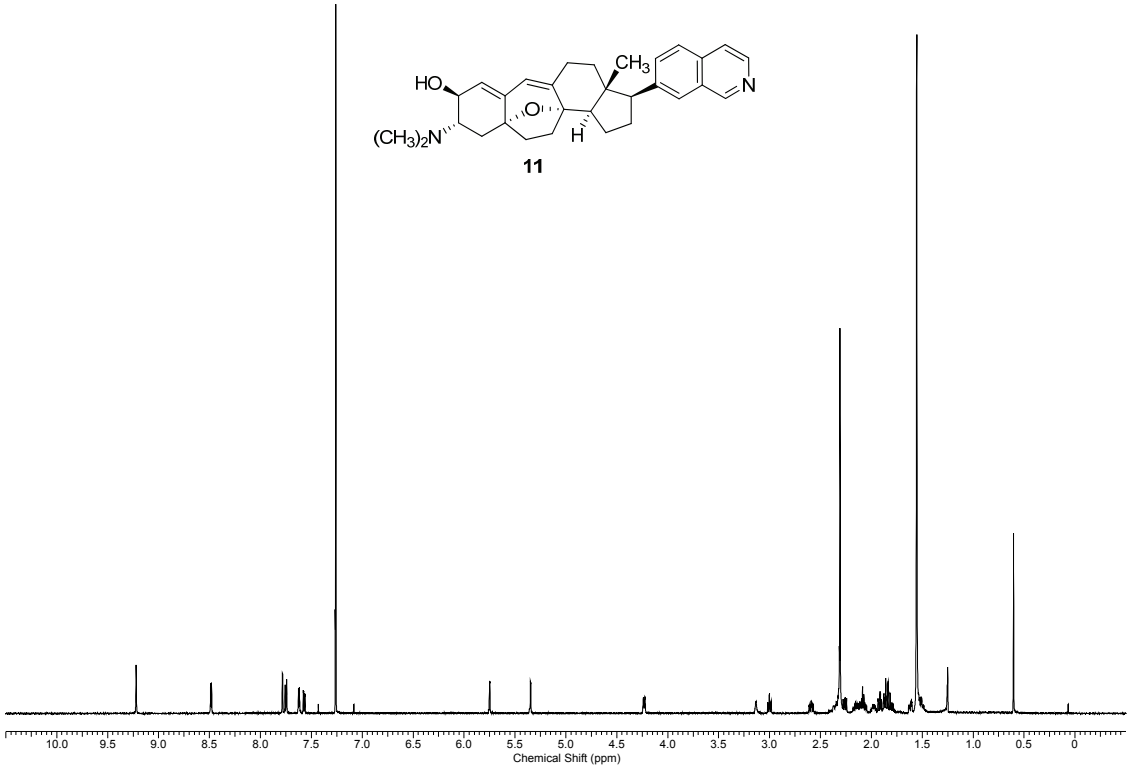


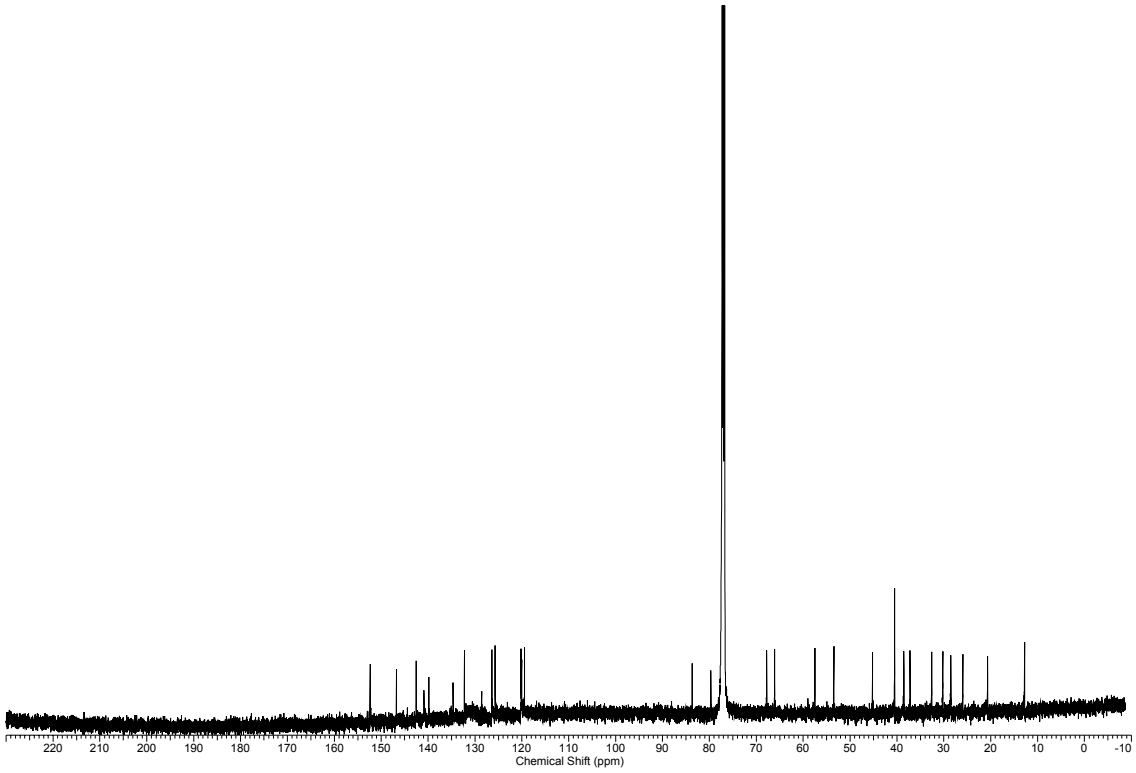
11

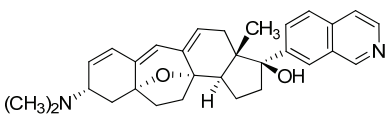
a) After Davisil® column

b) After HPLC (eliminated product removed)



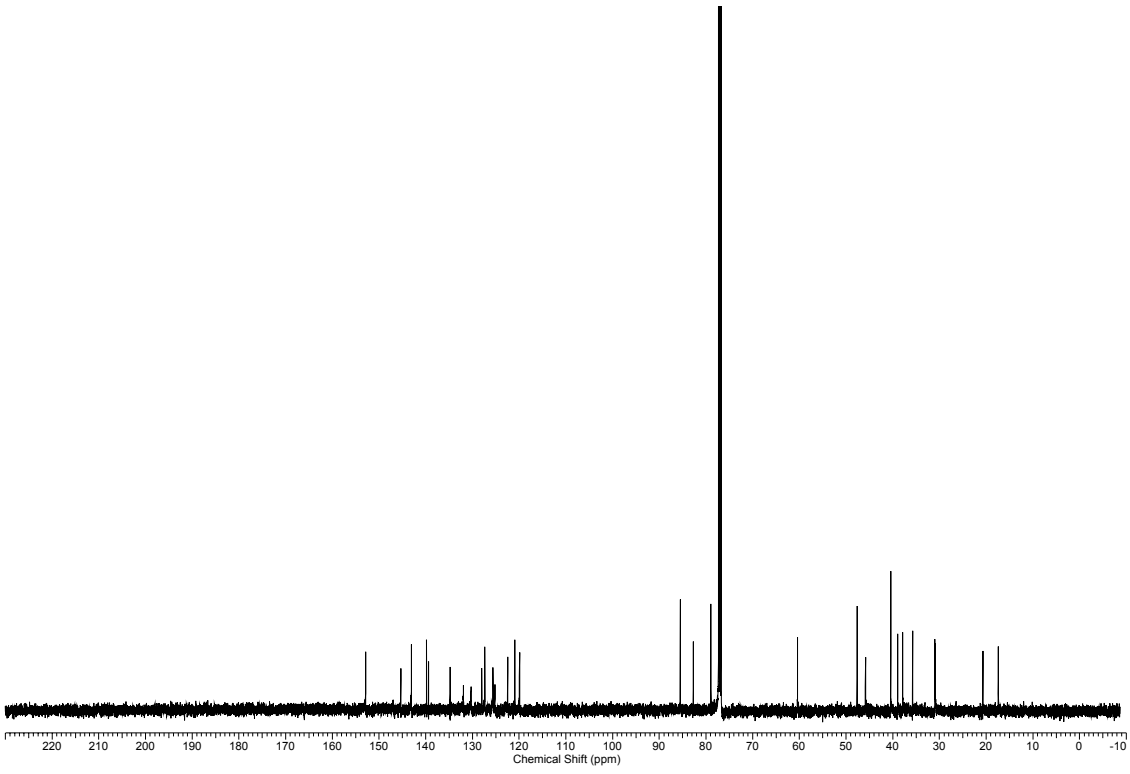

HO
(CH3)2N
O
H
CH3
N
11
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

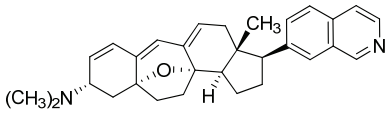

CH3
N
O
OH
H
(CH3)2N

161

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

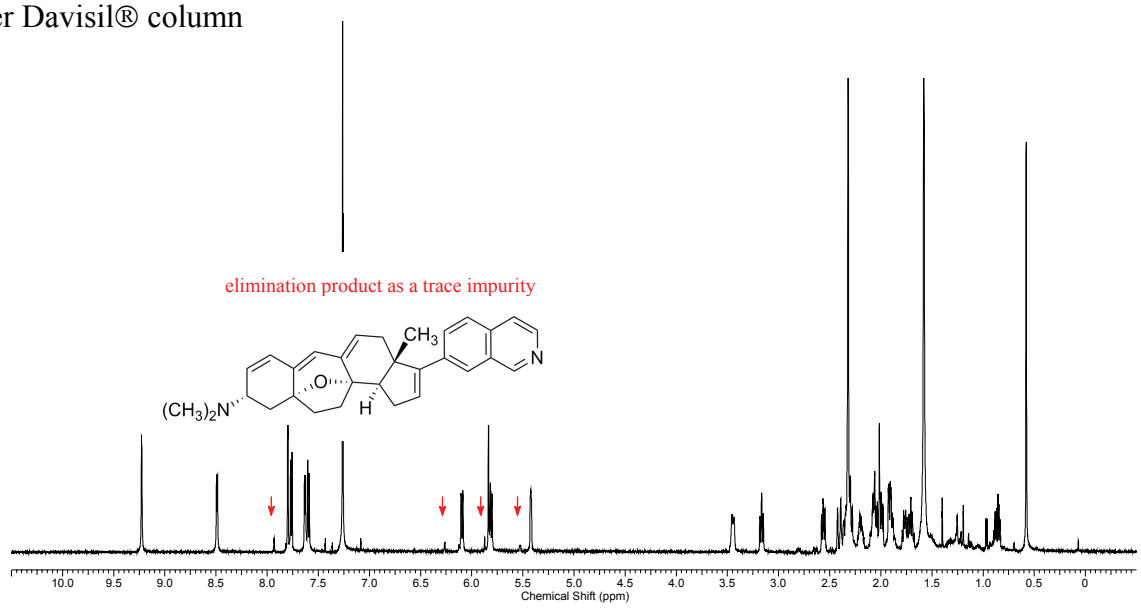

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

Purification of Cortistatin J (**9**).

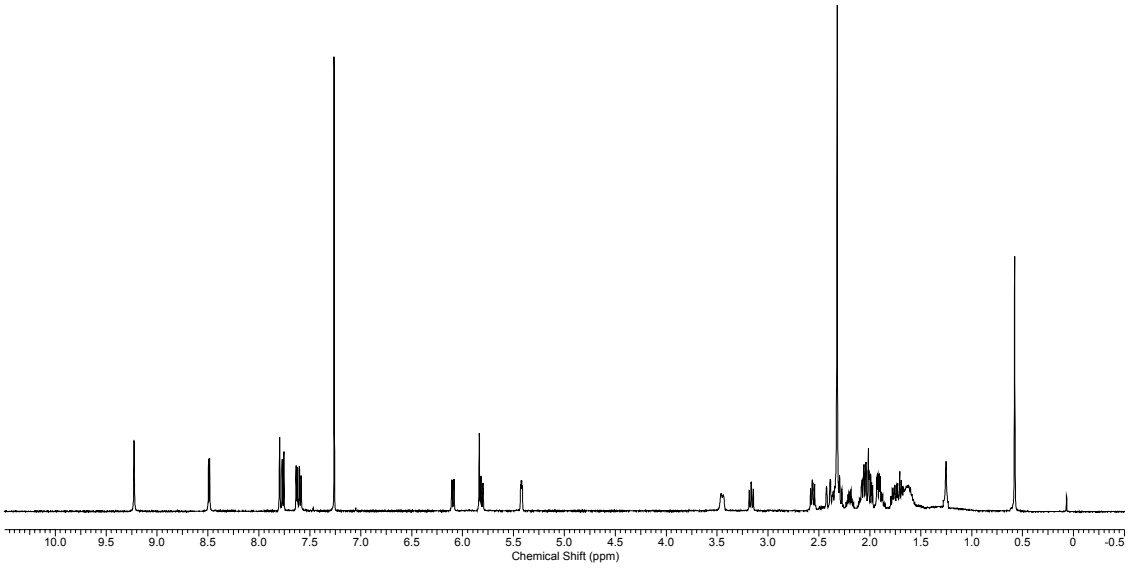


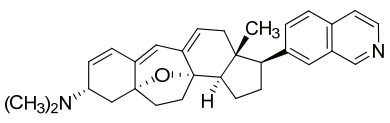
9

a) After Davisil® column



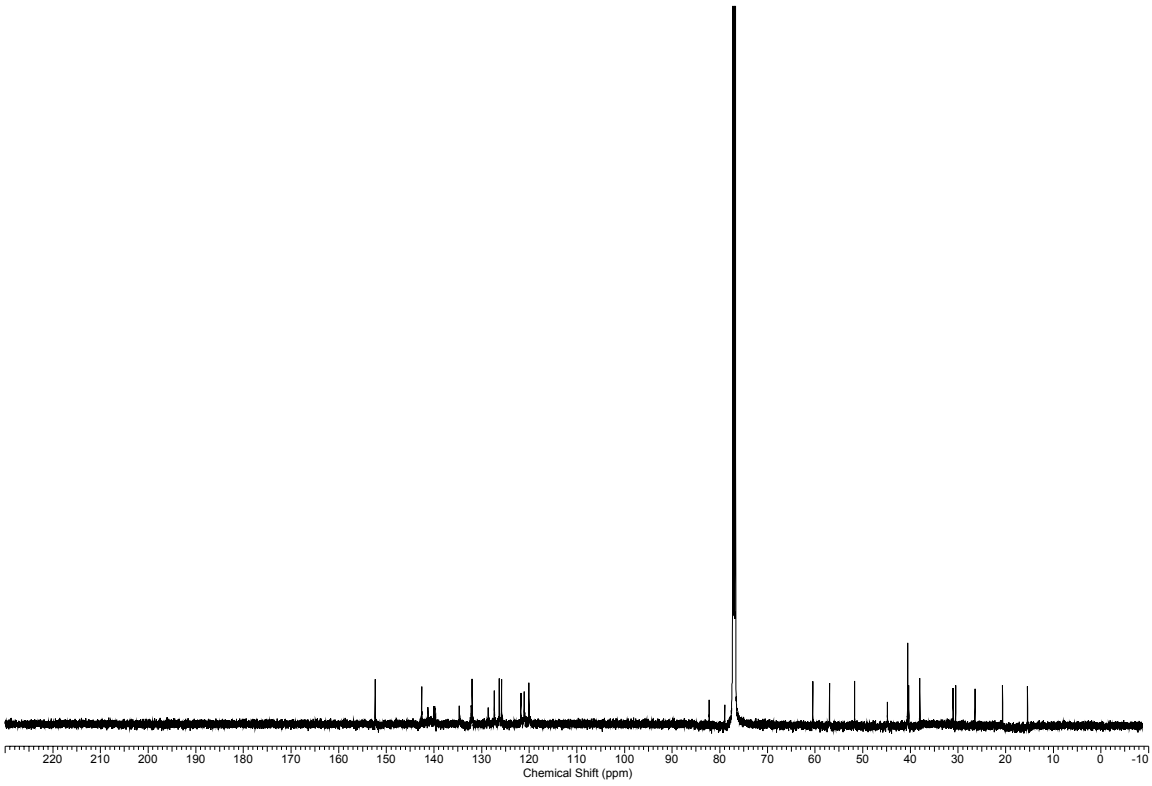
b) After HPLC (eliminated product removed)

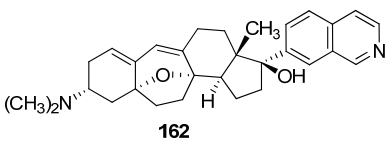



CH3
N
O
(CH3)2N
H

9

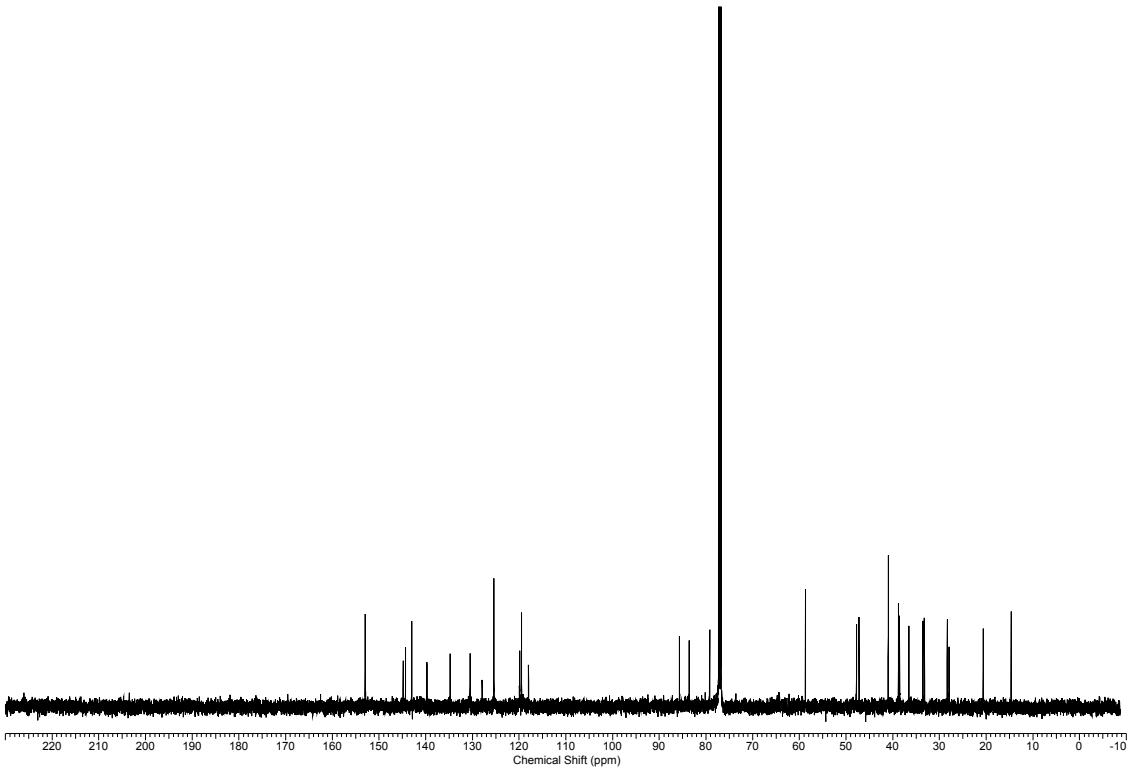
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5
Chemical Shift (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


CH3
N
O
OH
H
(CH3)2N

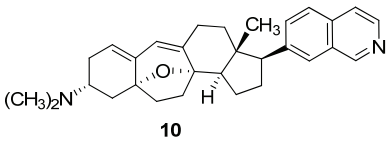
162

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

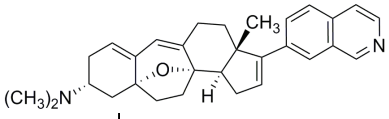
Purification of Cortistatin K (**10**).

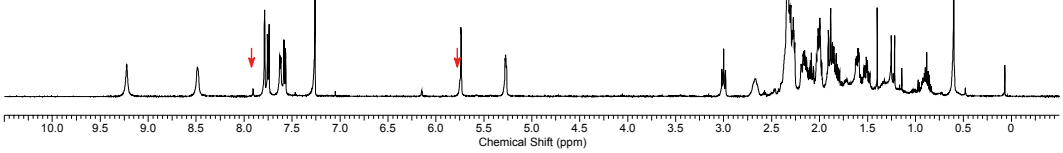
a) After Davisil® column



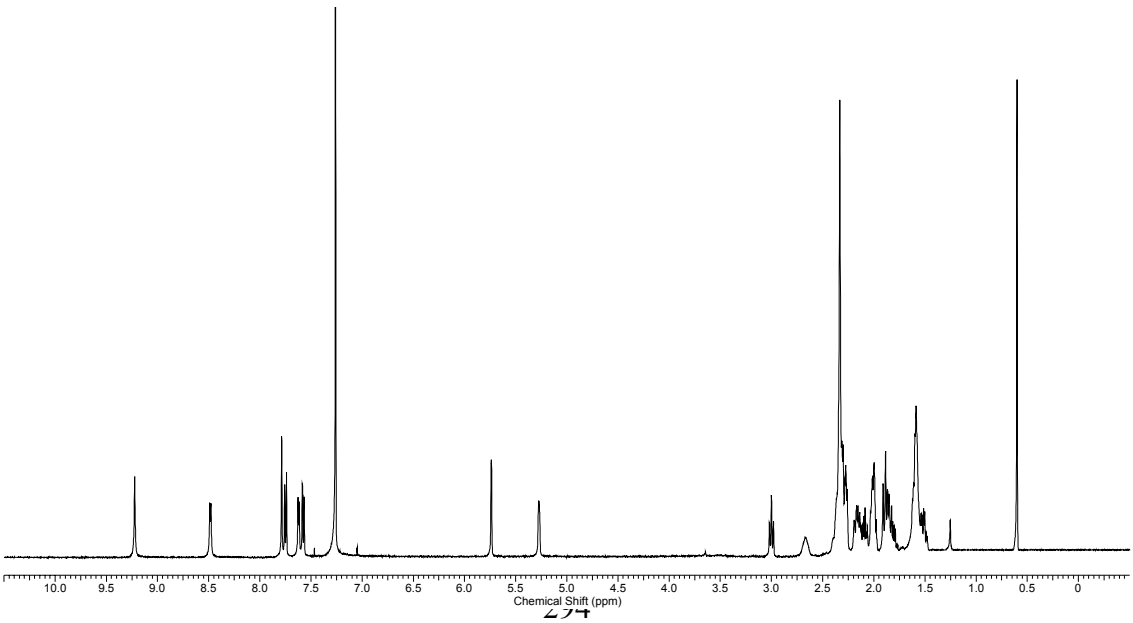
10

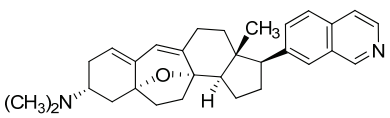
elimination product as a trace impurity





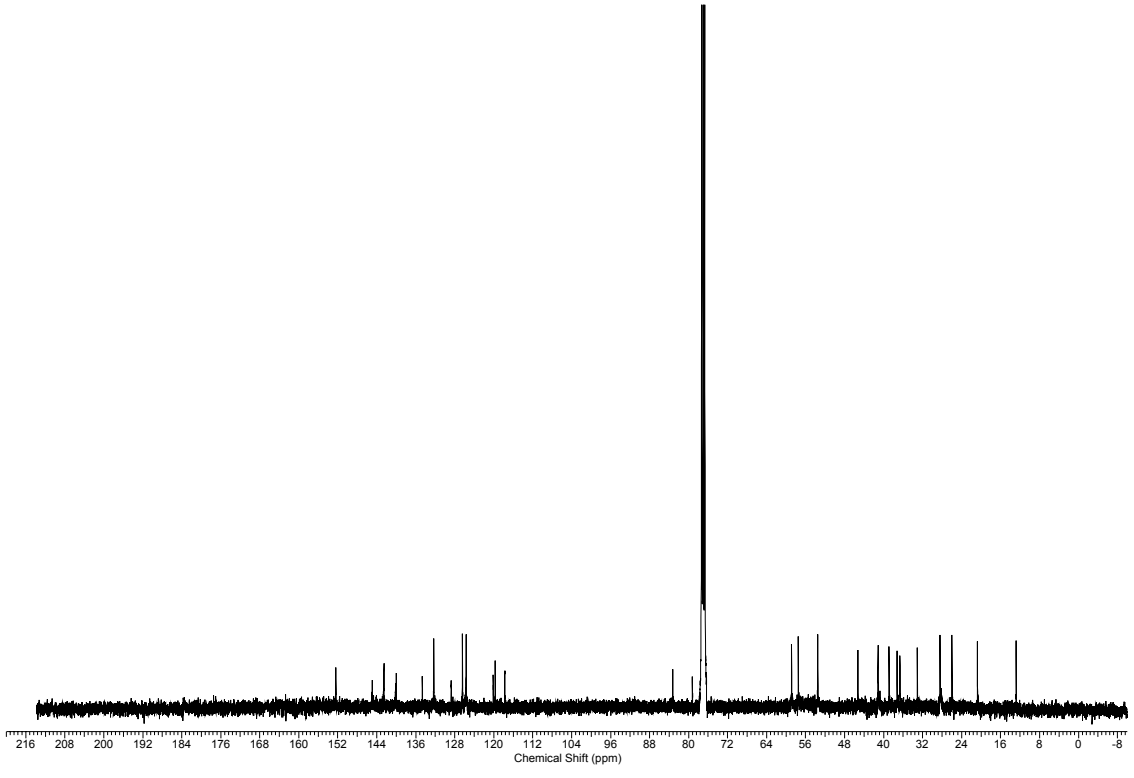
b) After HPLC (eliminated product removed)

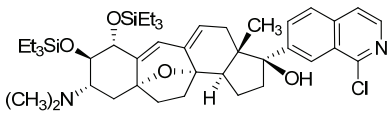



CH3
N
O
(CH3)2N
H

10

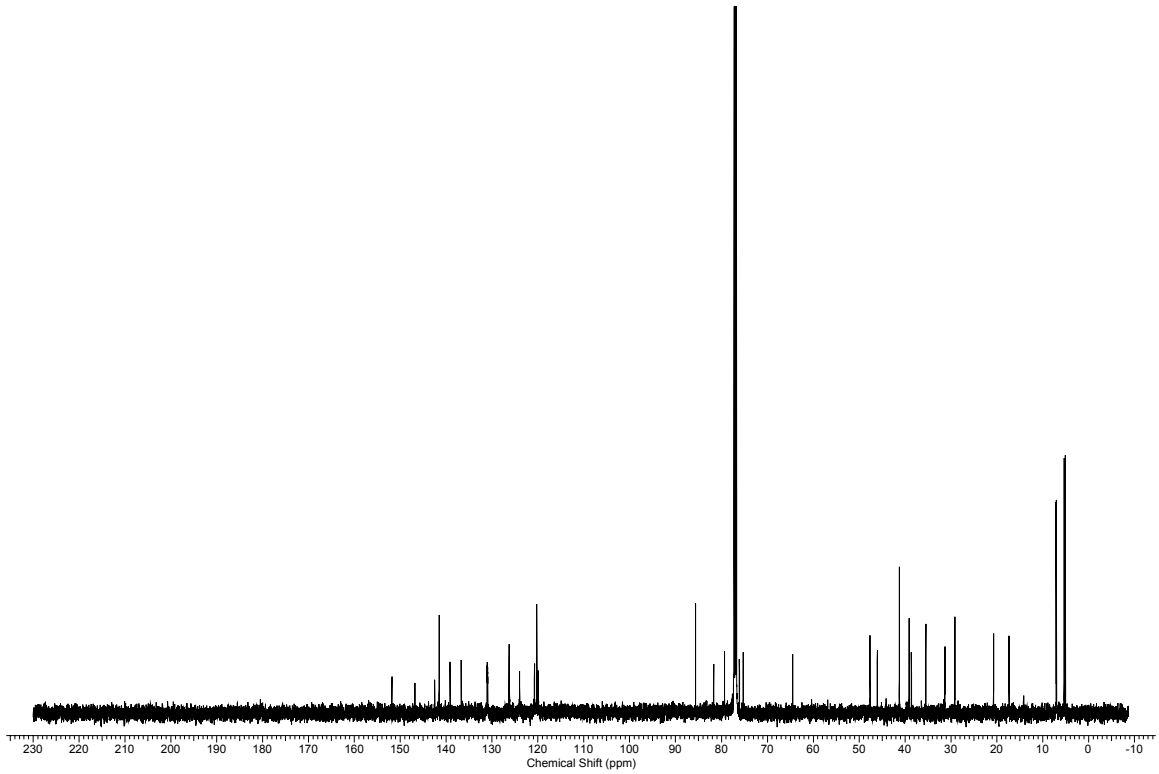
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

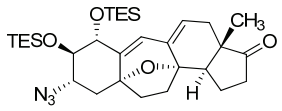

216 208 200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0 -8
Chemical Shift (ppm)


OSiEt3
CH3
Et3SiO
N
O
OH
(CH3)2N
H
Cl

169

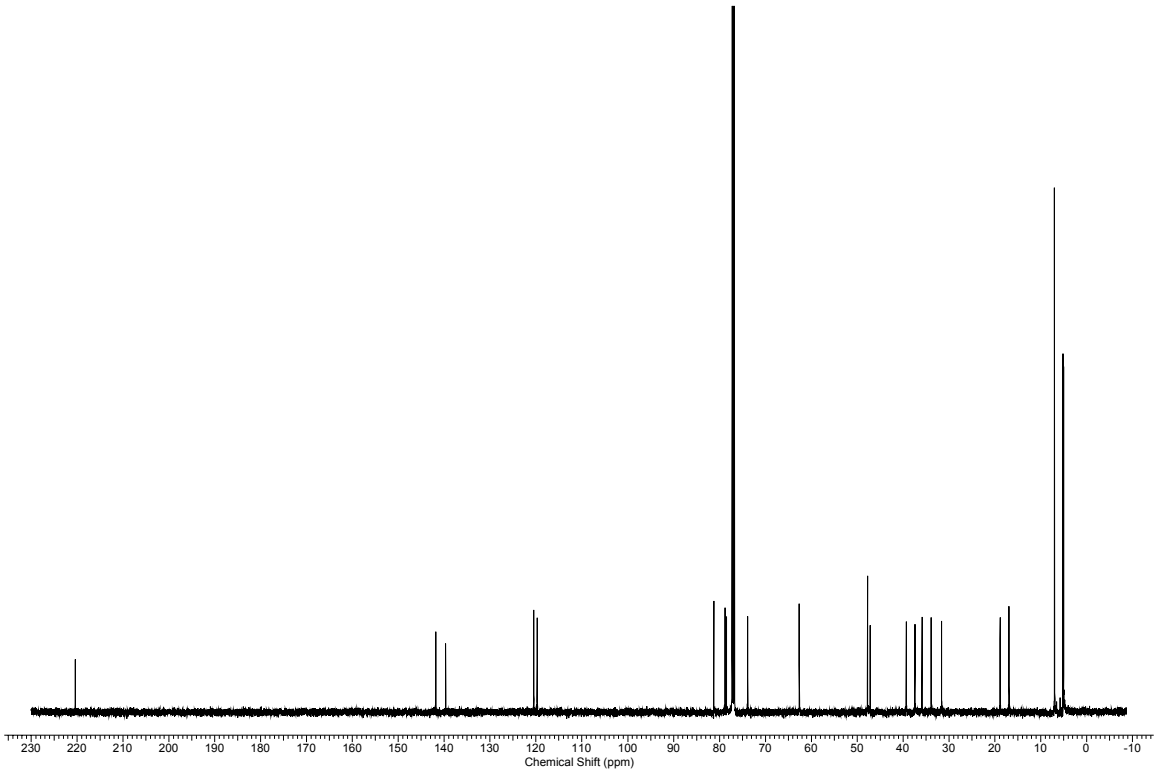
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5
Chemical Shift (ppm)

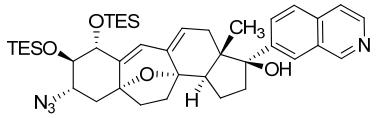

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


OTES
TESO
N_3
O
H
CH_3
O

171

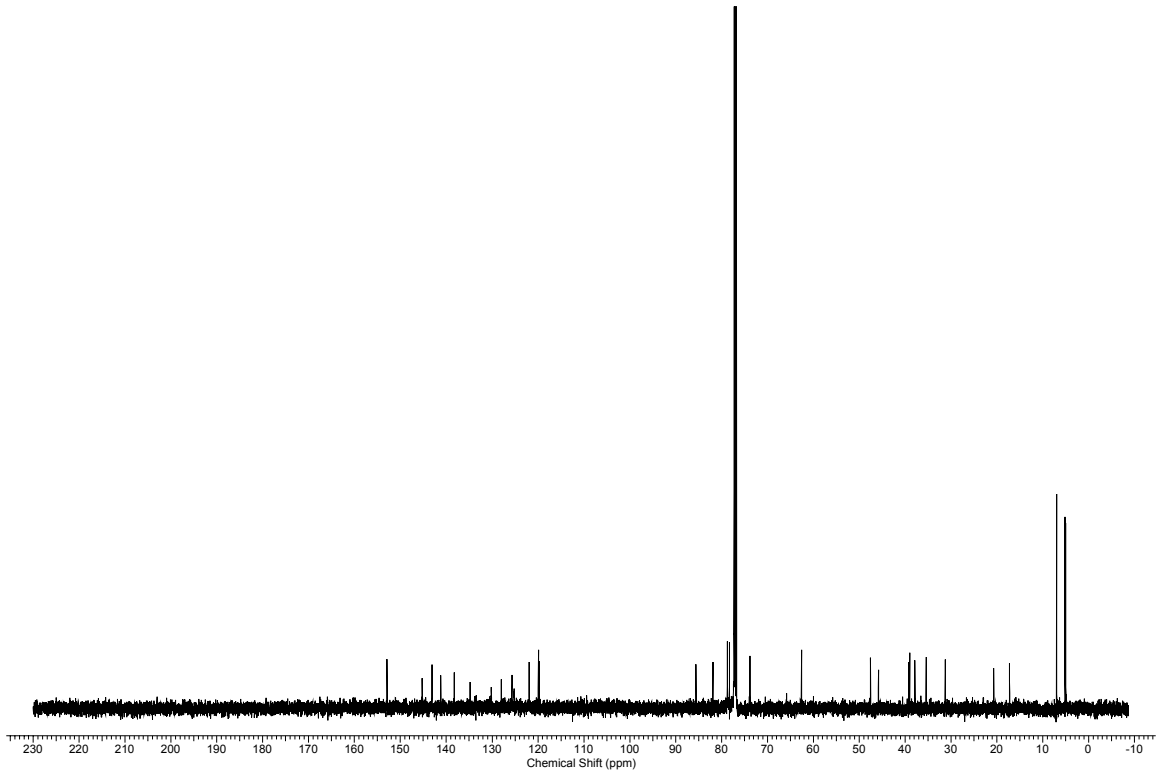
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5 -1.0
Chemical Shift (ppm)

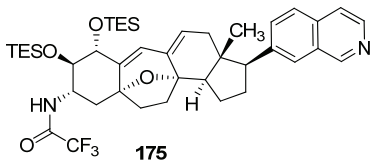

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


OTES
TESO
CH_3
N
O
OH
N_3
H

172

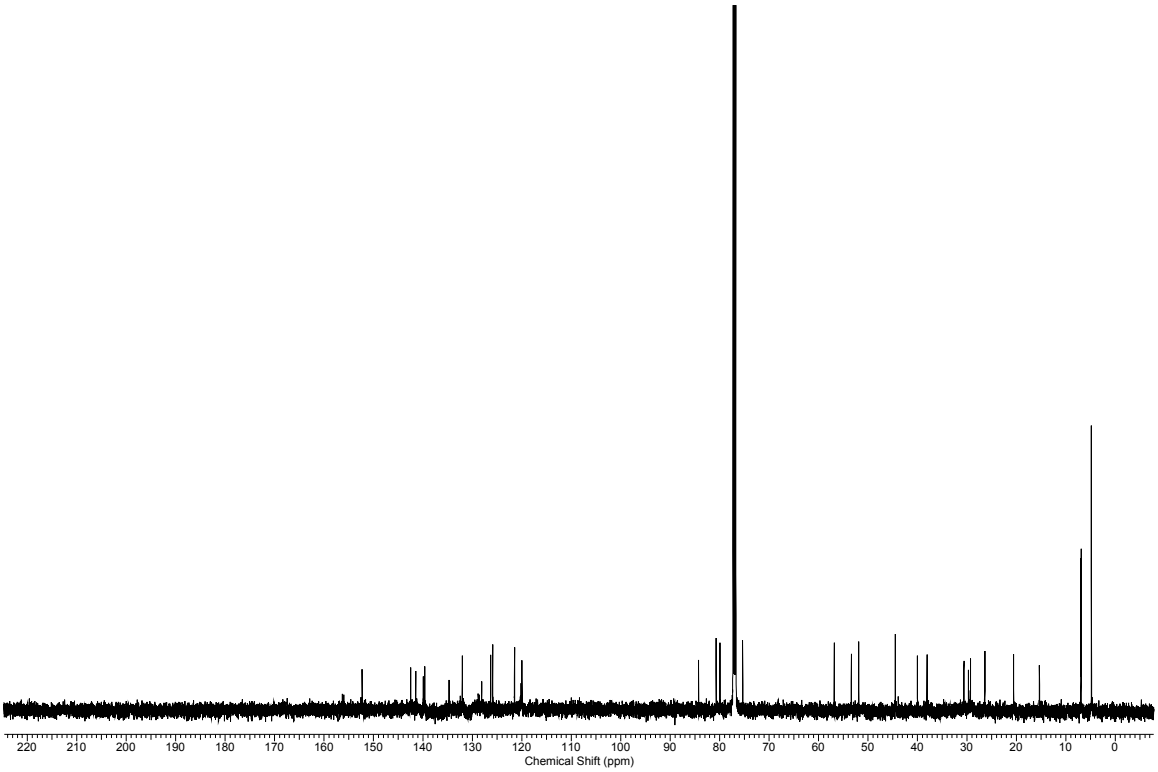
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5
Chemical Shift (ppm)

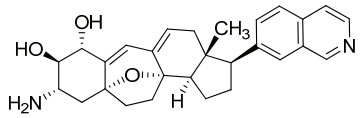

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


OTES
TESO
HN
O
CF3
CH3
N
O
H

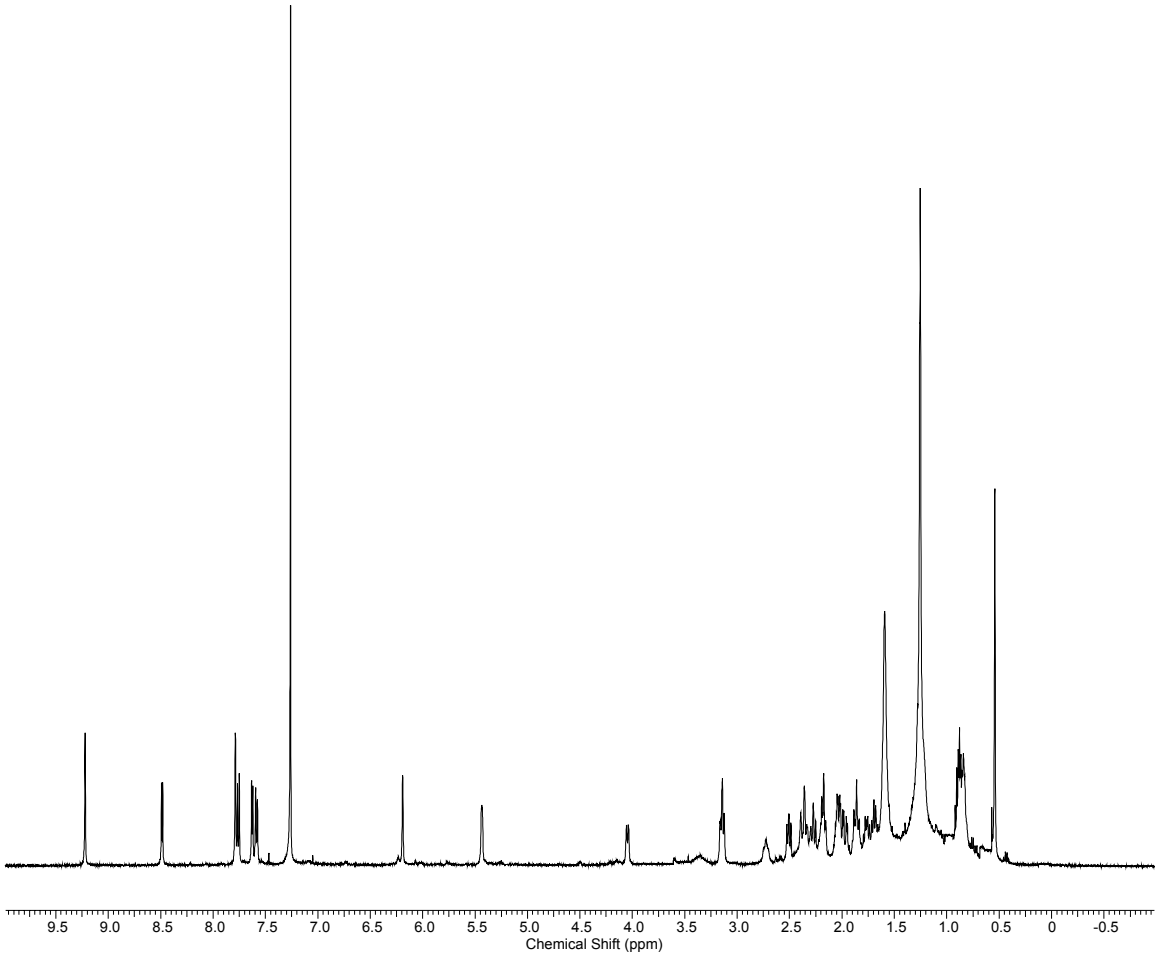
175

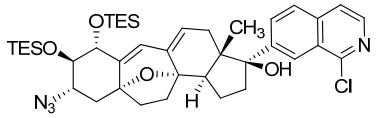
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5
Chemical Shift (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)


OH
HO
CH3
N
O
H2N
H

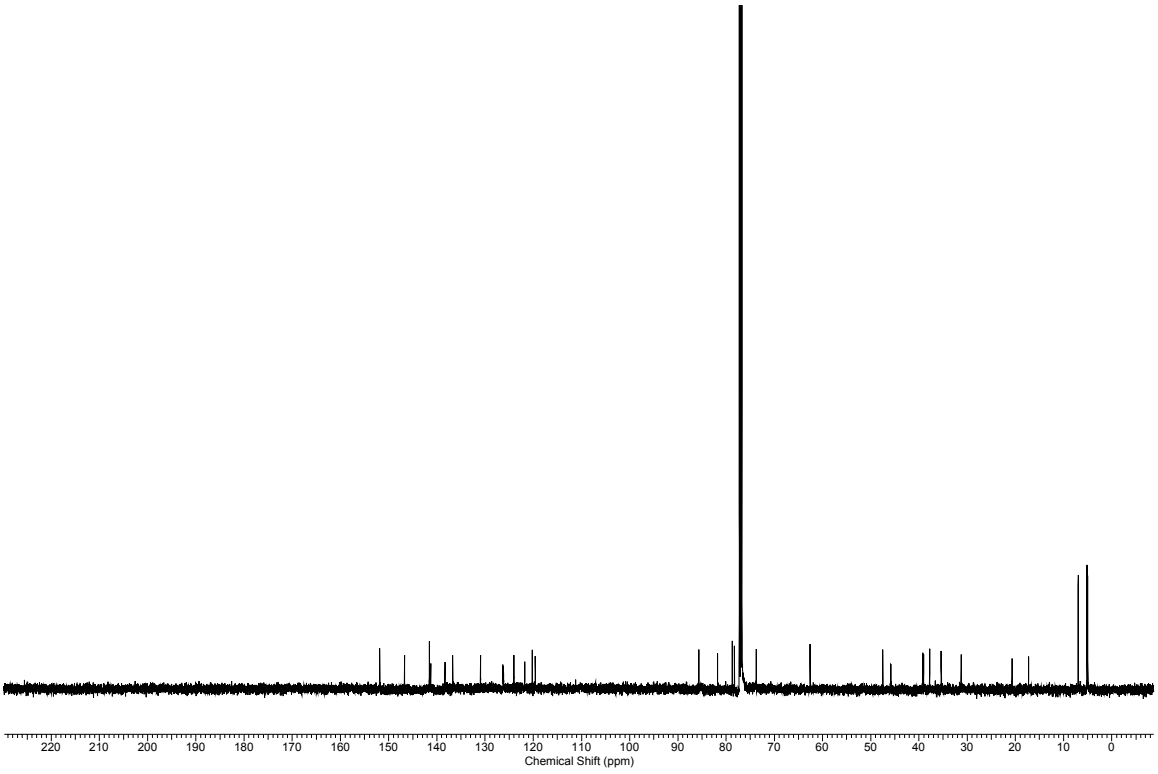
176

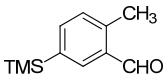

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5
Chemical Shift (ppm)


OTES
TESO
CH3
N
OH
O
Cl
N3
H

177

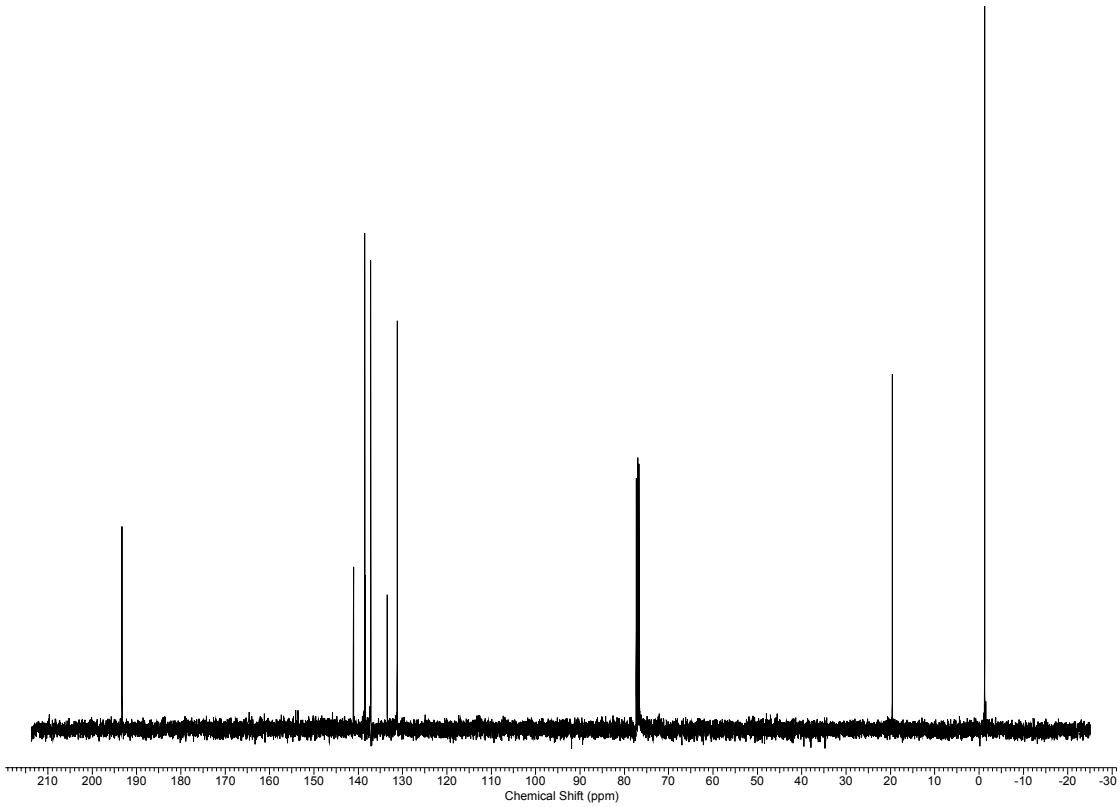
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5 -1.0
Chemical Shift (ppm)

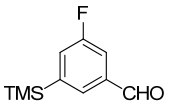

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
Chemical Shift (ppm)


CH3
TMS
CHO

222

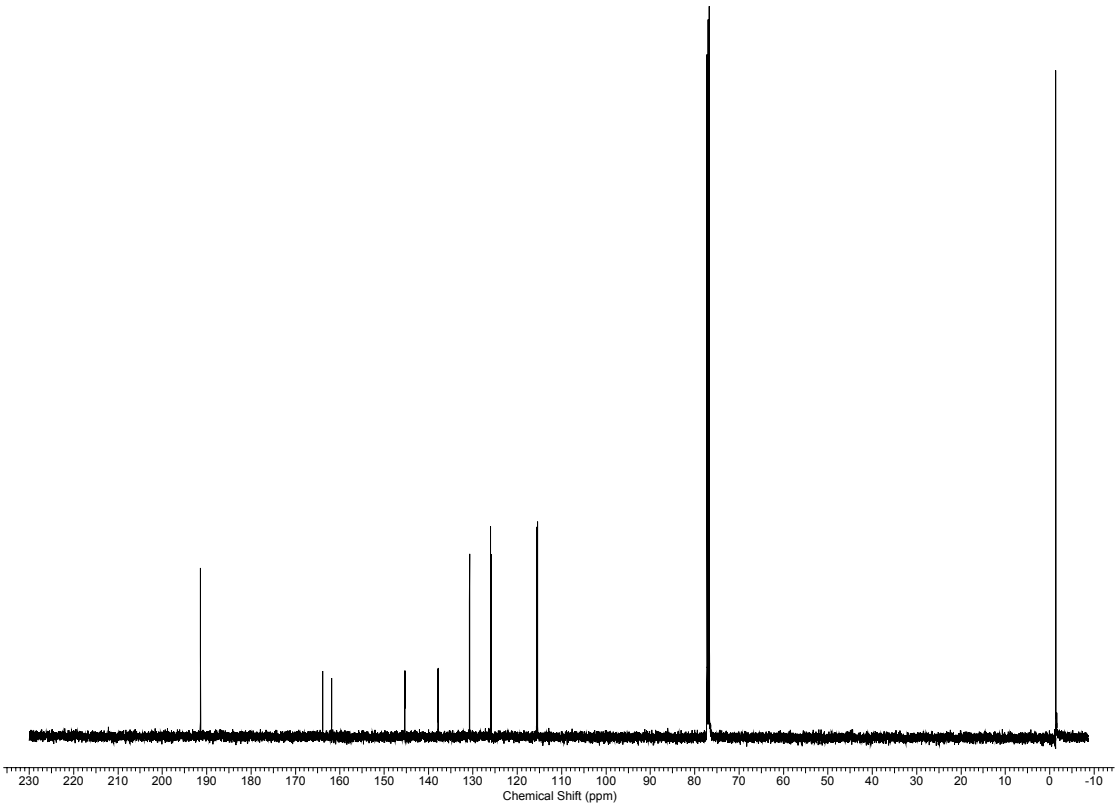
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

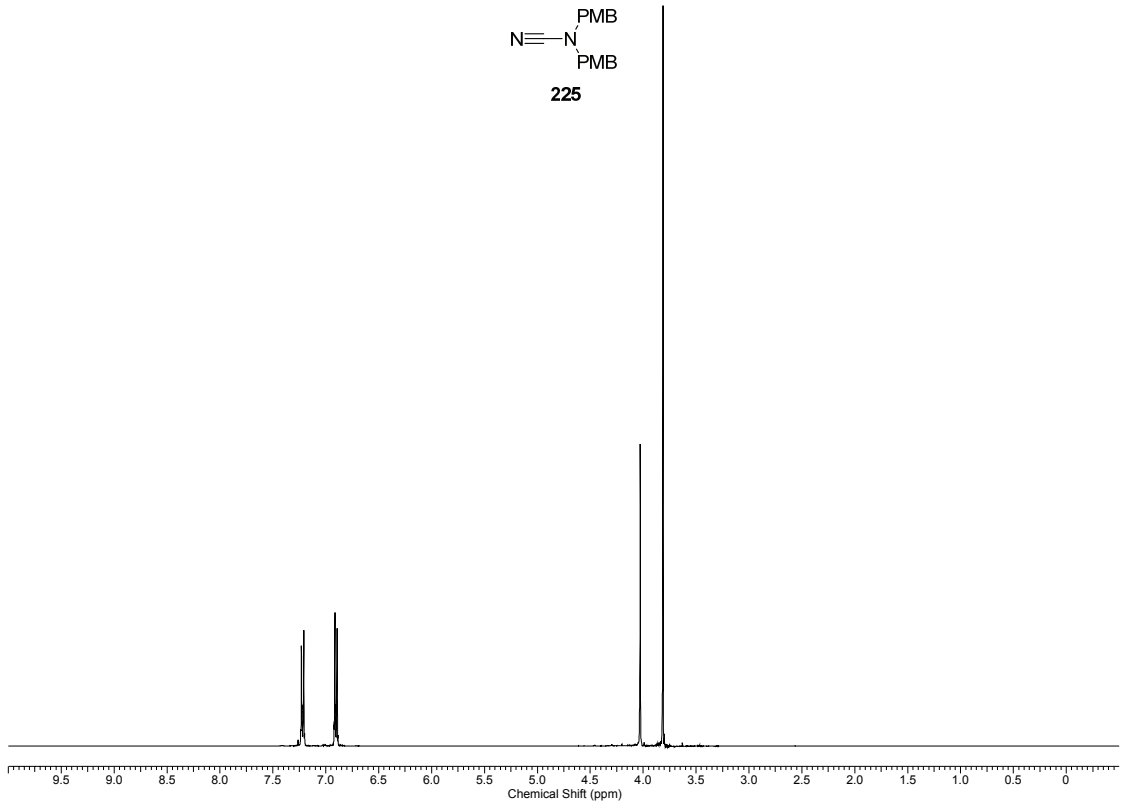

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
Chemical Shift (ppm)

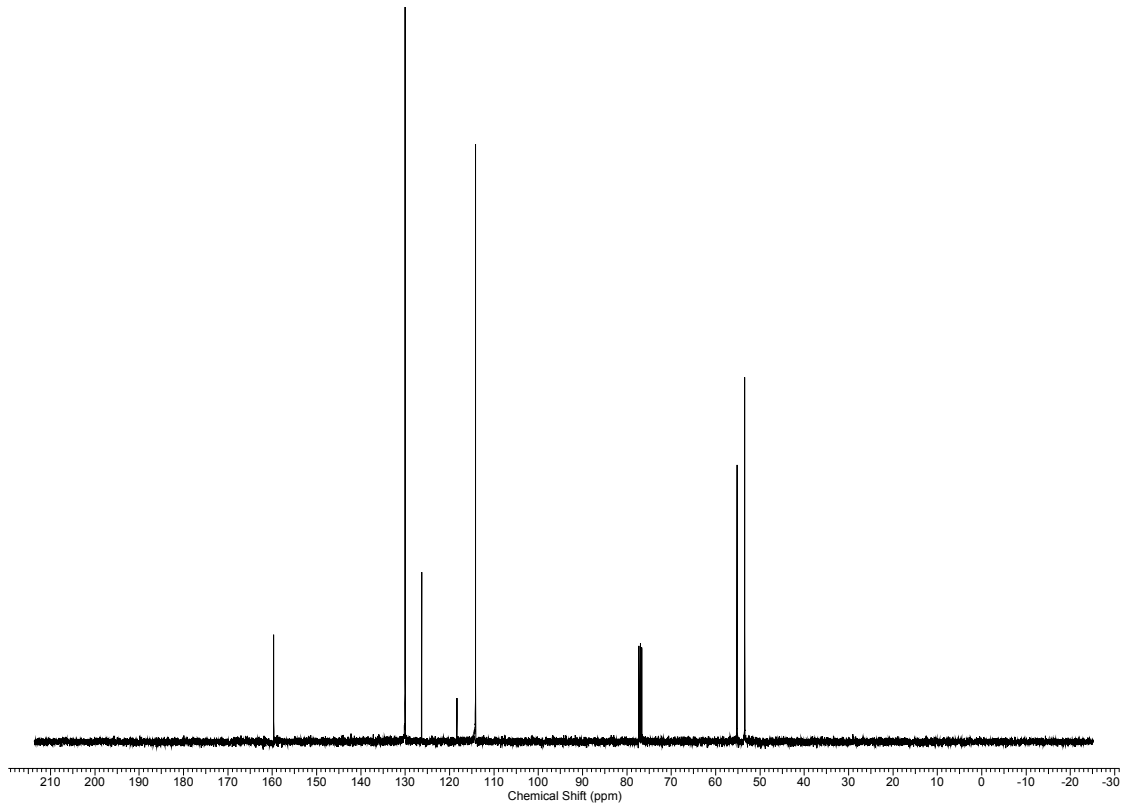

F
TMS
CHO

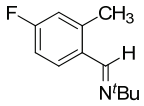
224

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

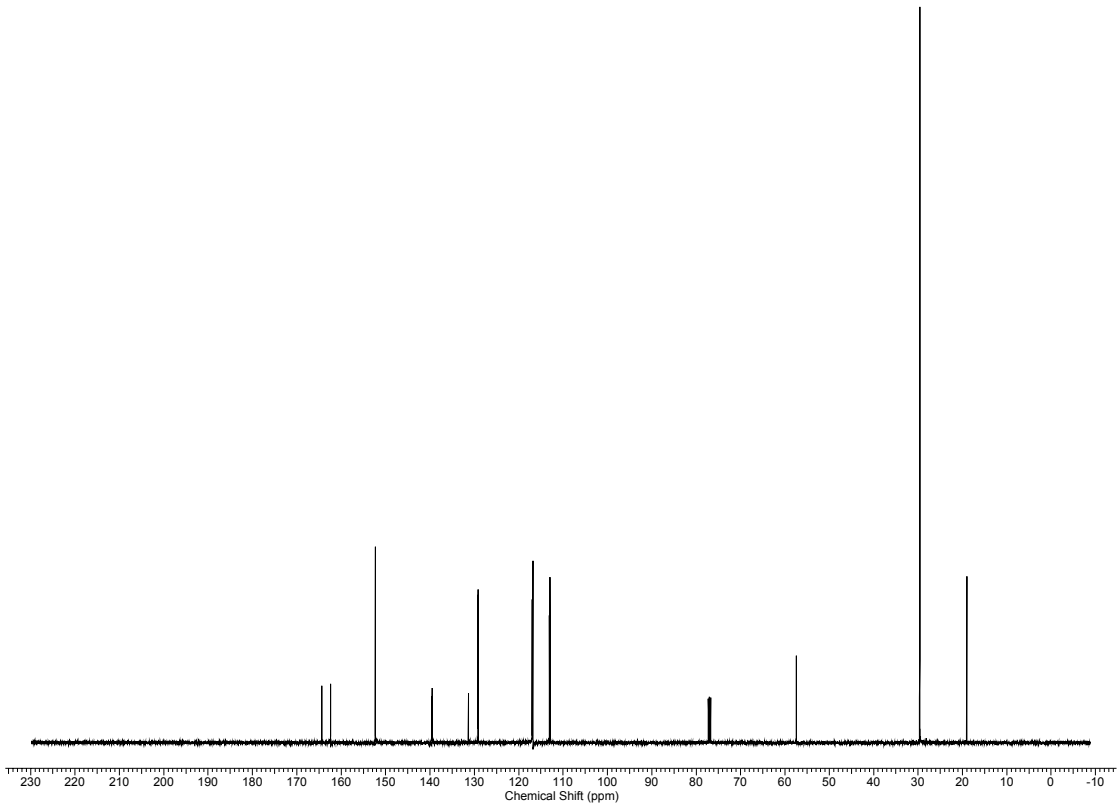

PMB
N
N
PMB
225
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

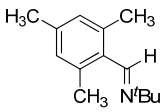

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
Chemical Shift (ppm)


F
CH3
H
N
tBu

226

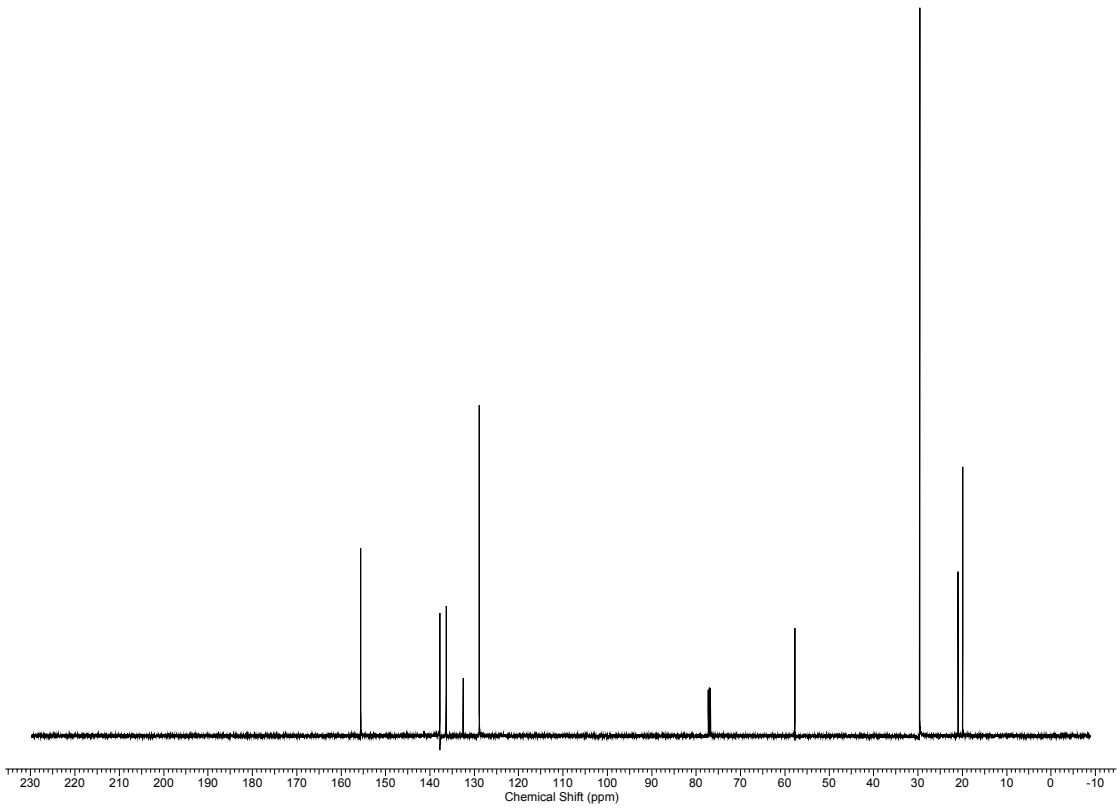
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

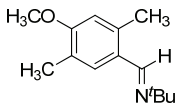

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


H3C
CH3
H
CH3
N
tBu

227

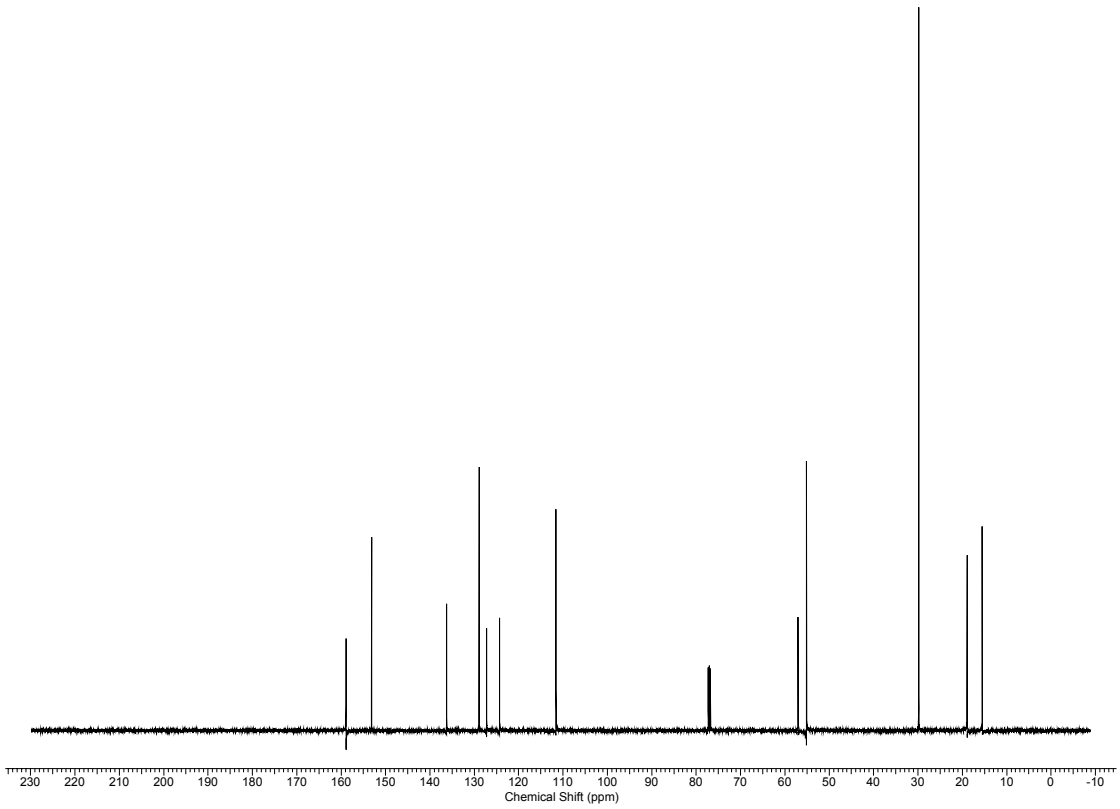
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

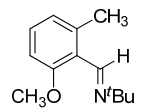

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


H3CO
CH3
H3C
H
NtBu

228

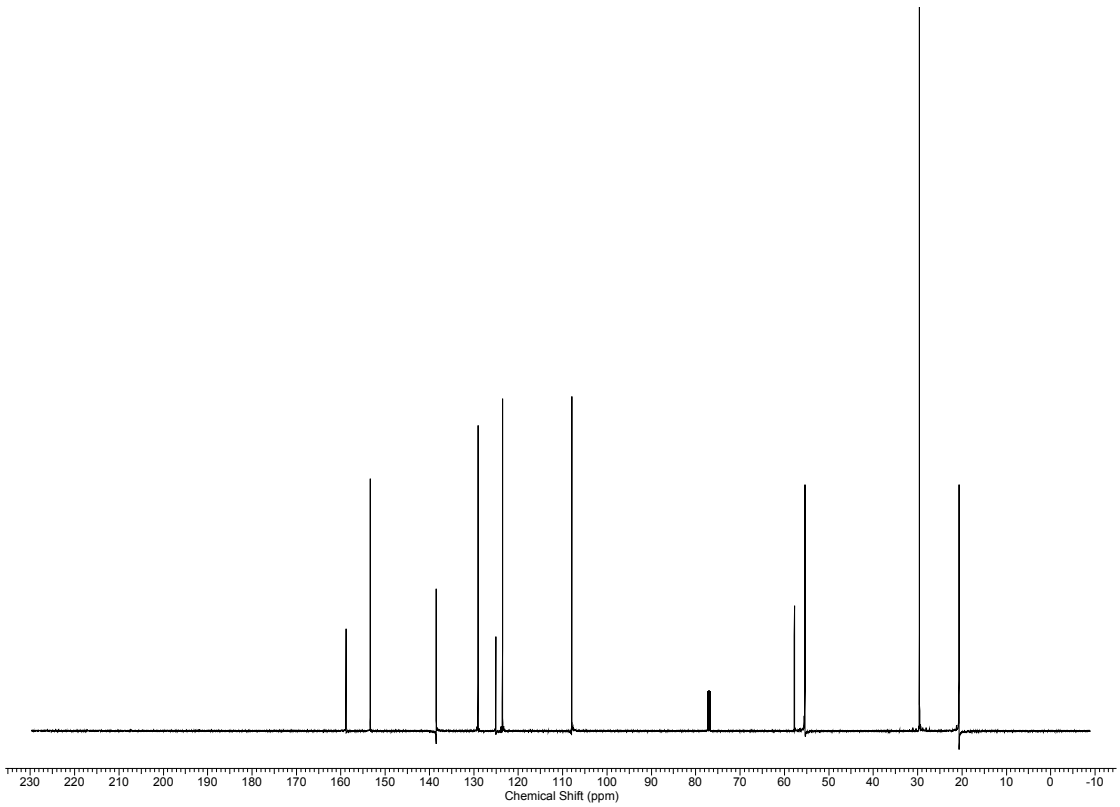
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

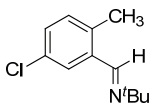

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


CH3
H
CH3O
NtBu

229

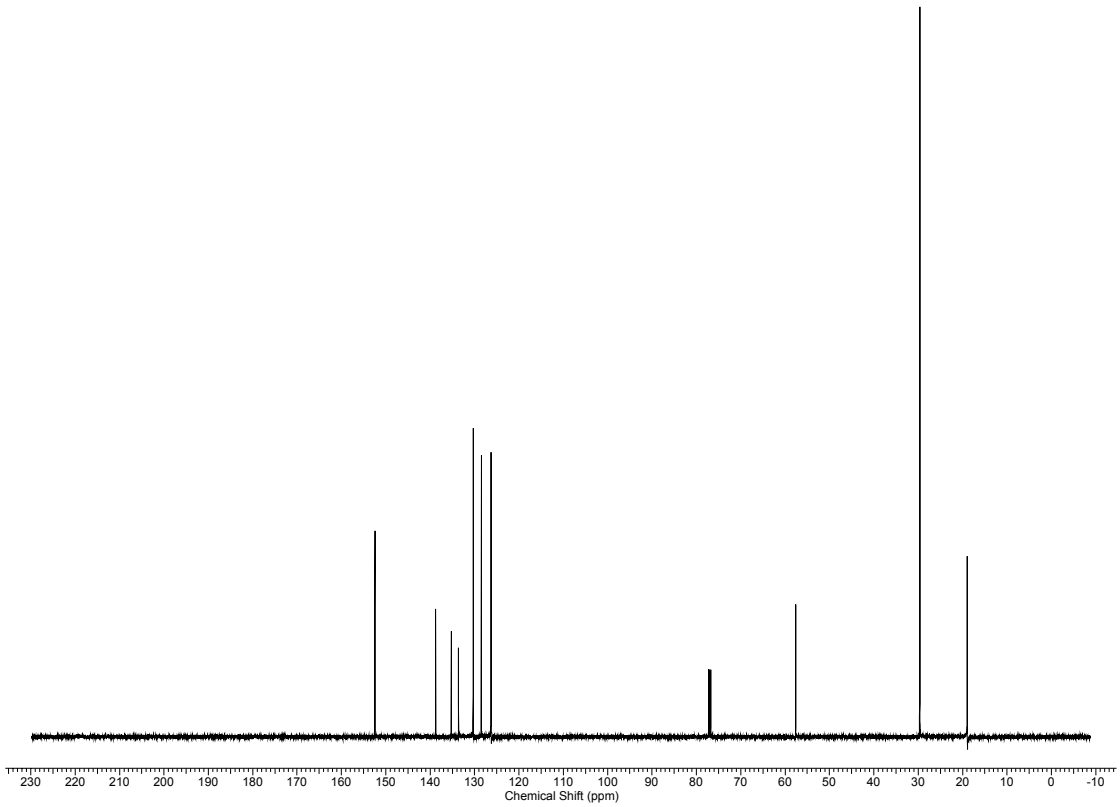
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

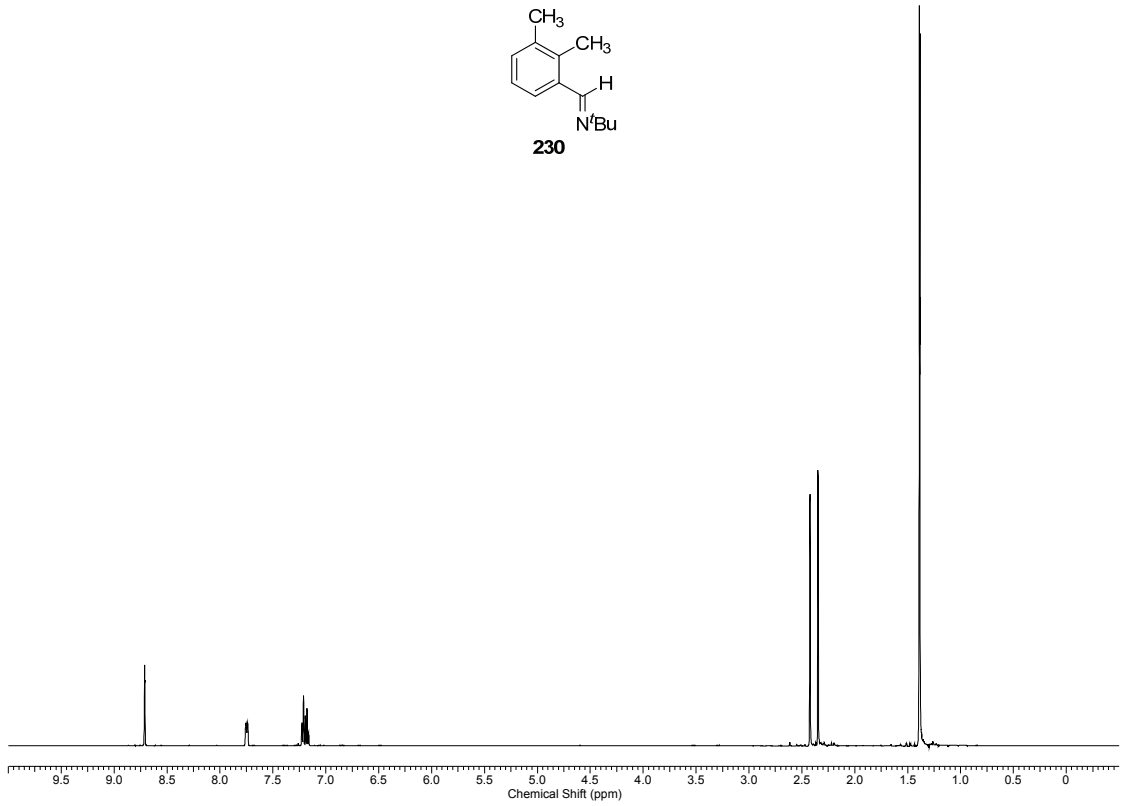

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


CH3
H
Cl
N^{t}Bu

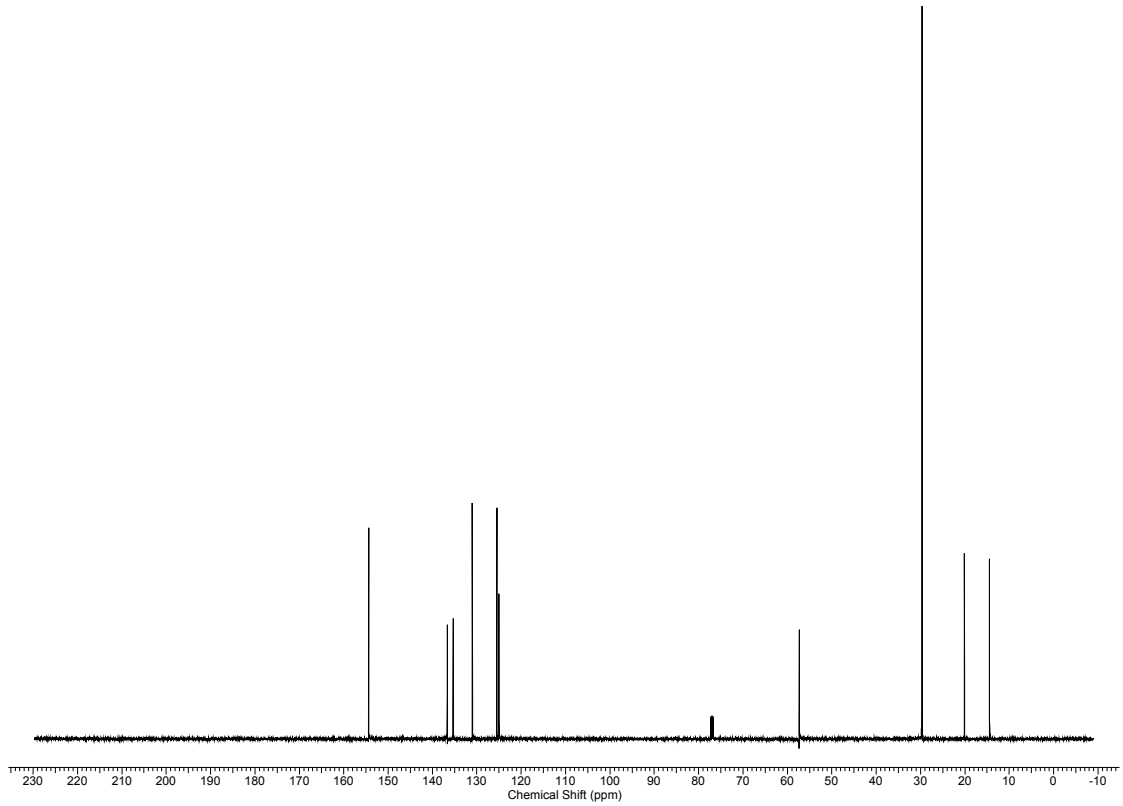
216

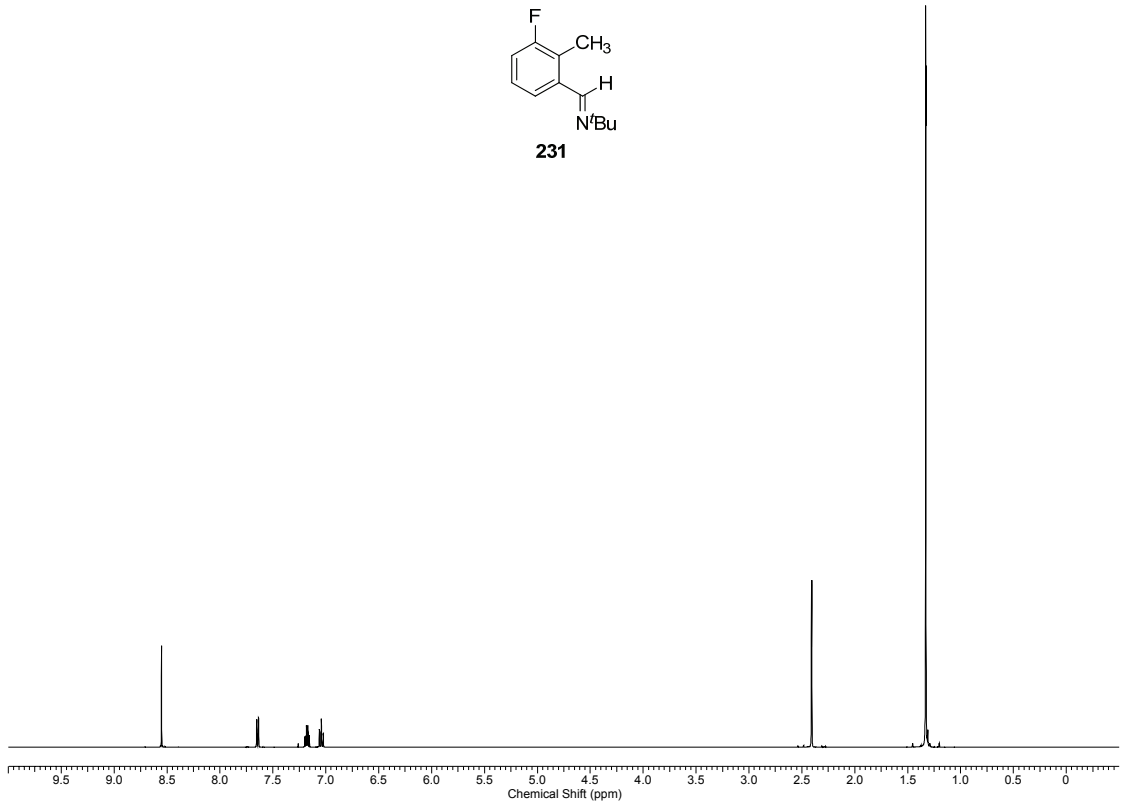
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

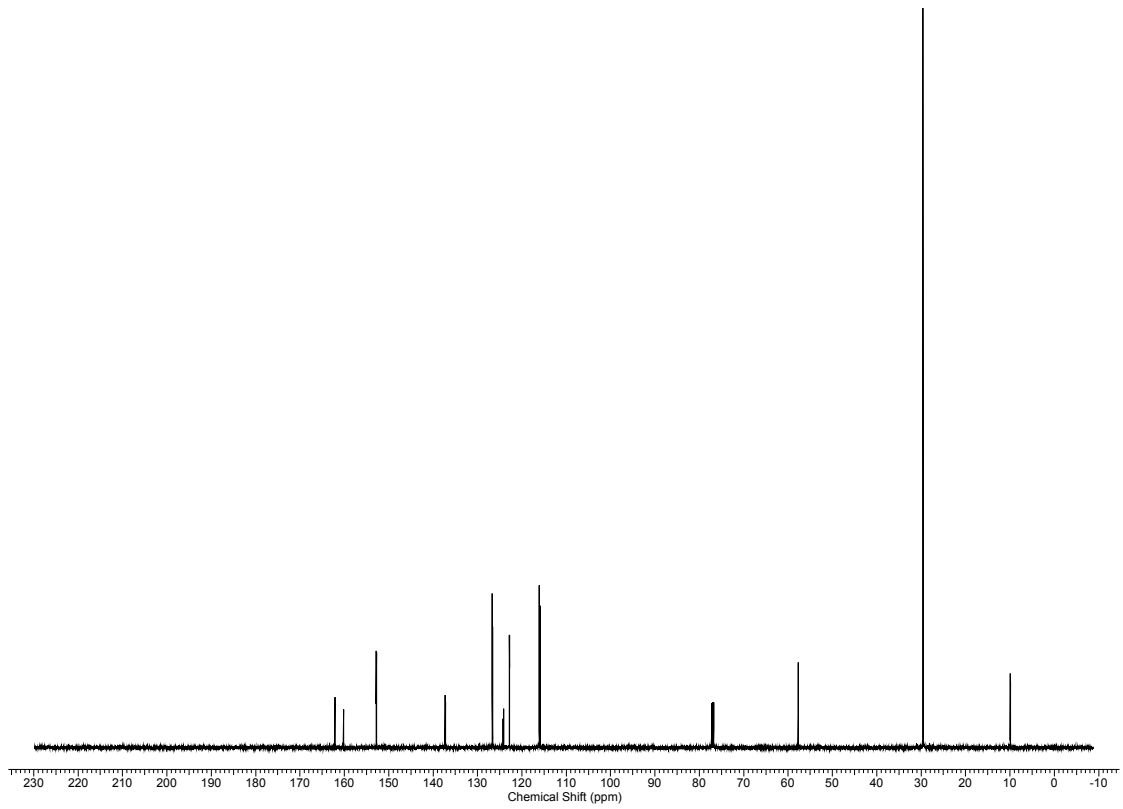

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

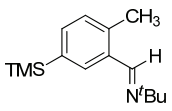

CH3
CH3
H
N
tBu
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

230


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

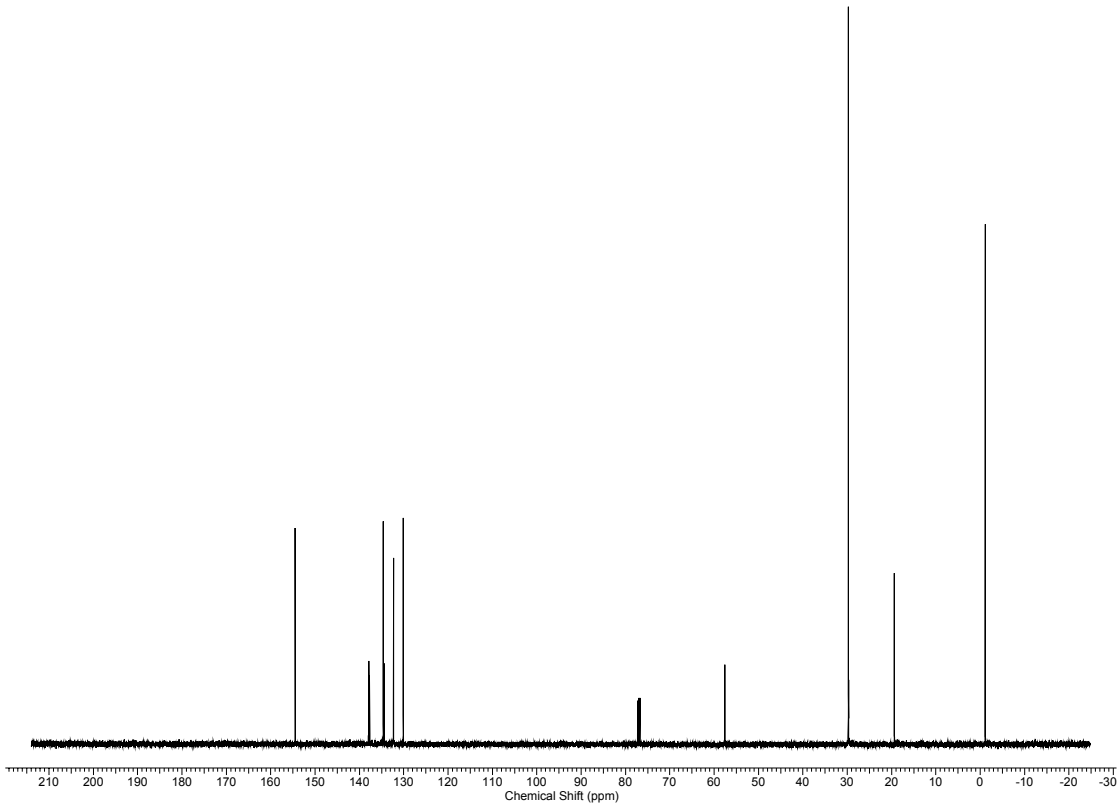

F
CH3
H
N
tBu
231
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

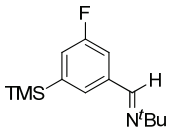

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


CH3
H
TMS
N^{t}Bu

232

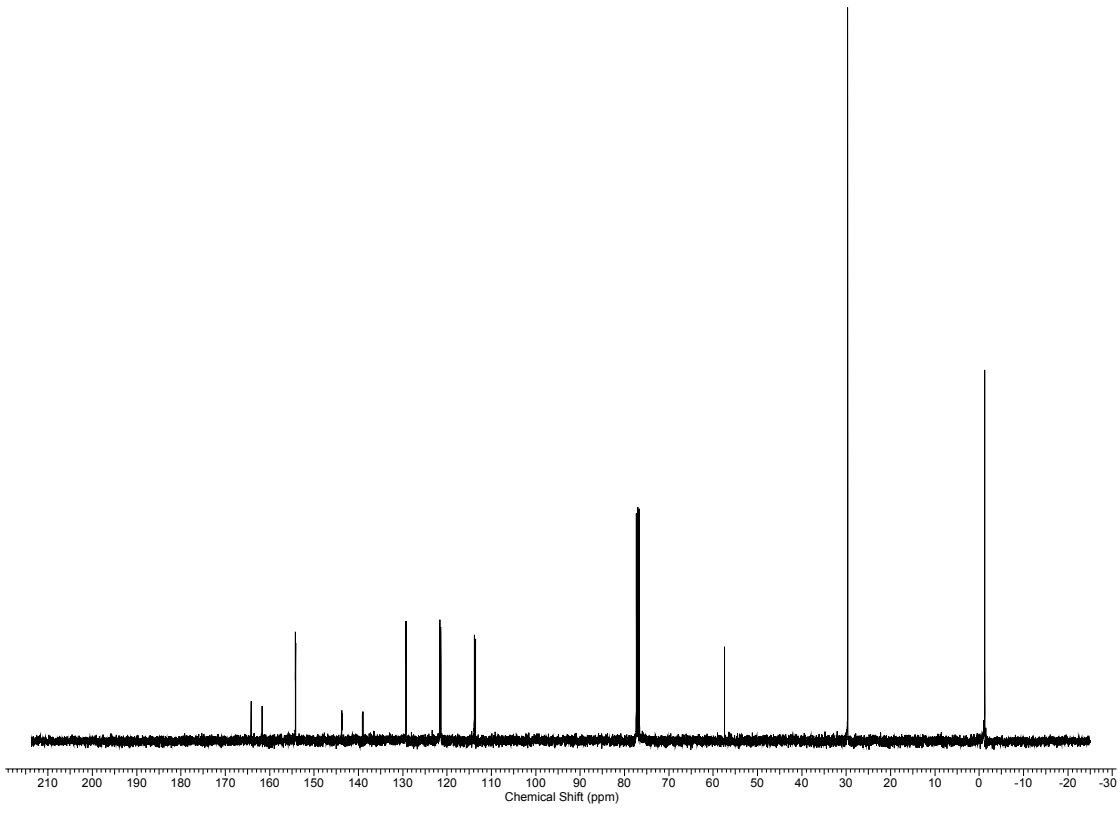
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

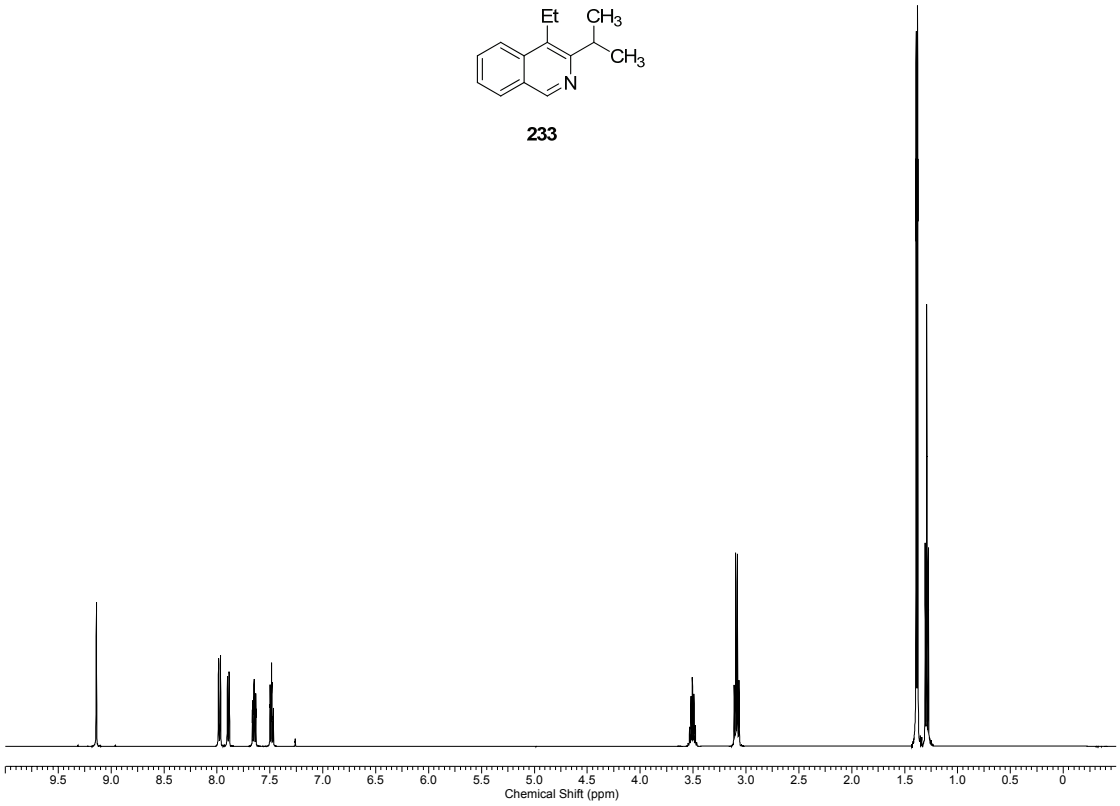

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
Chemical Shift (ppm)


F
TMS
H
N^{t}Bu

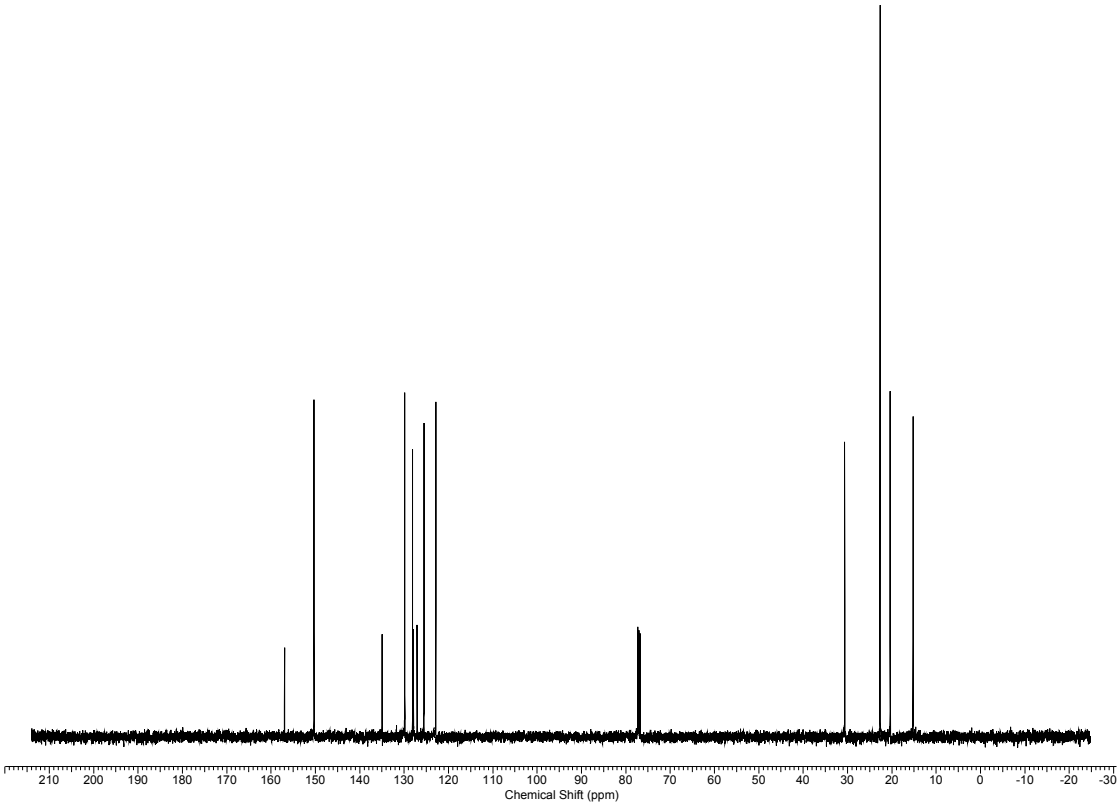
206

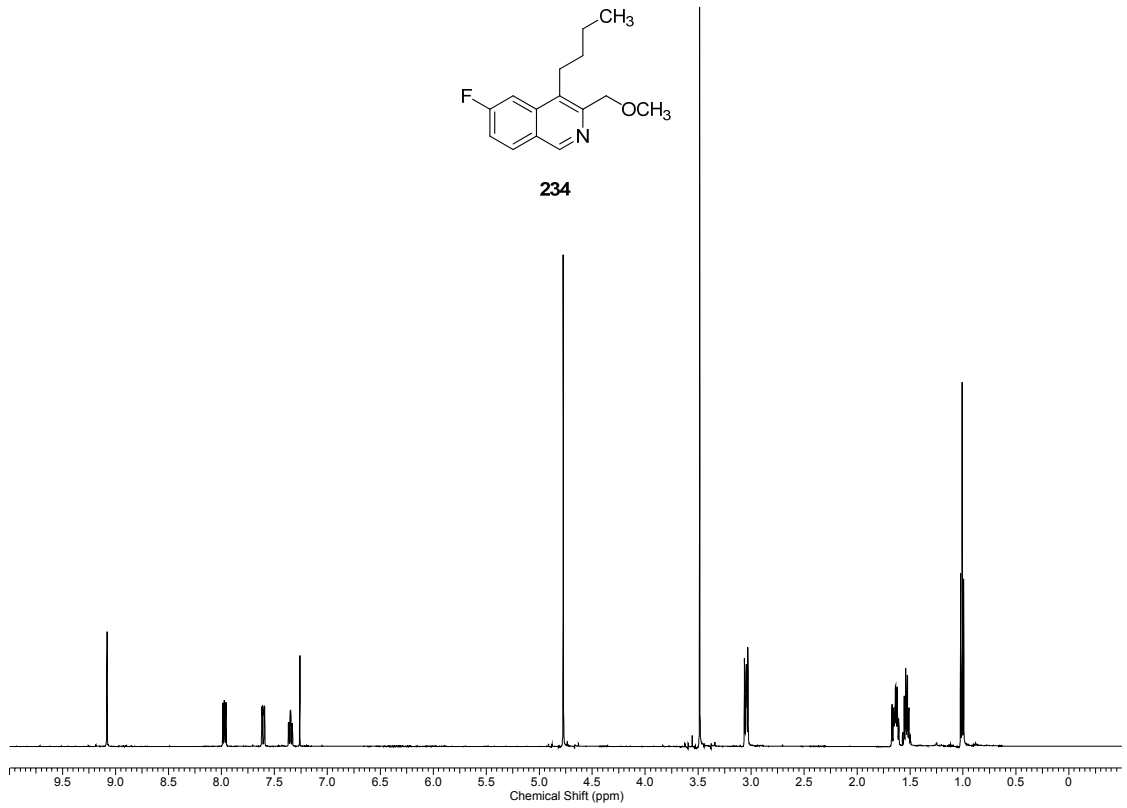
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
Chemical Shift (ppm)

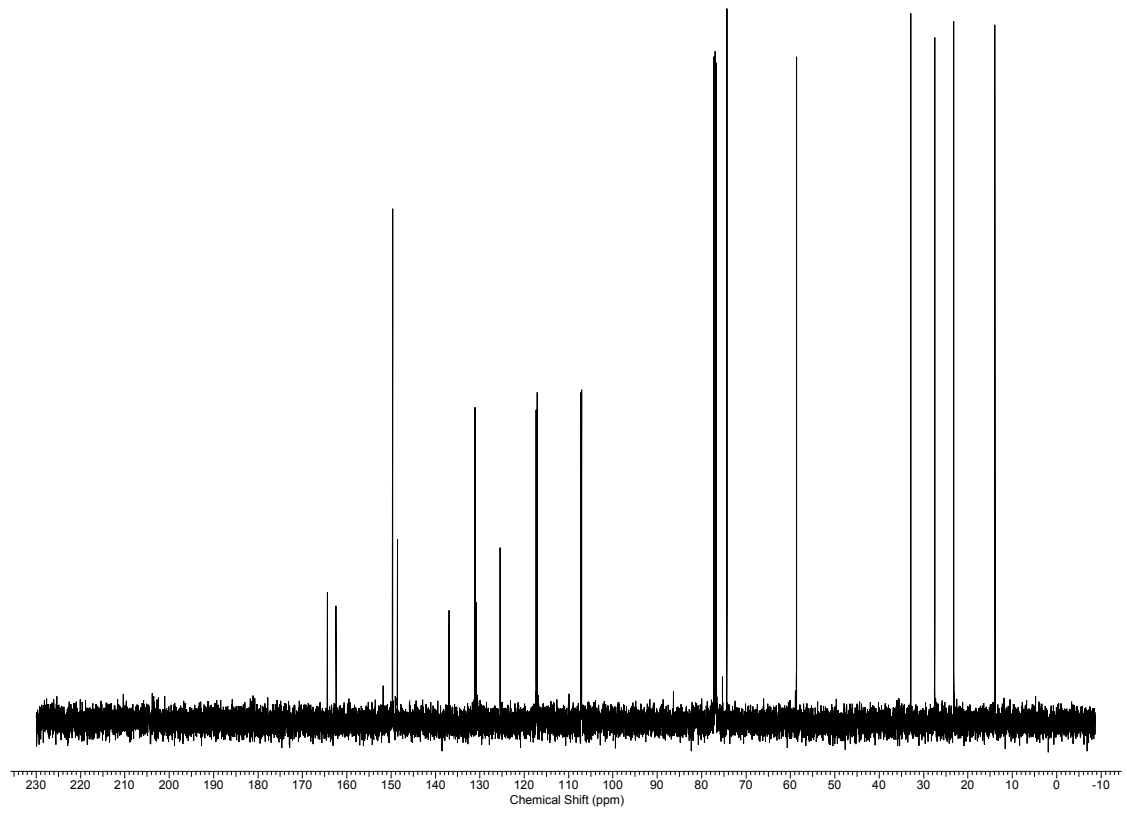

Et
CH3
CH3
N
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

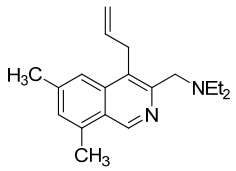
233


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
Chemical Shift (ppm)

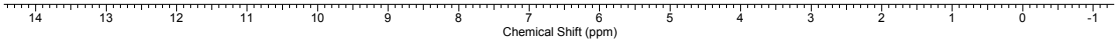

CH3
F
OCH3
N
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

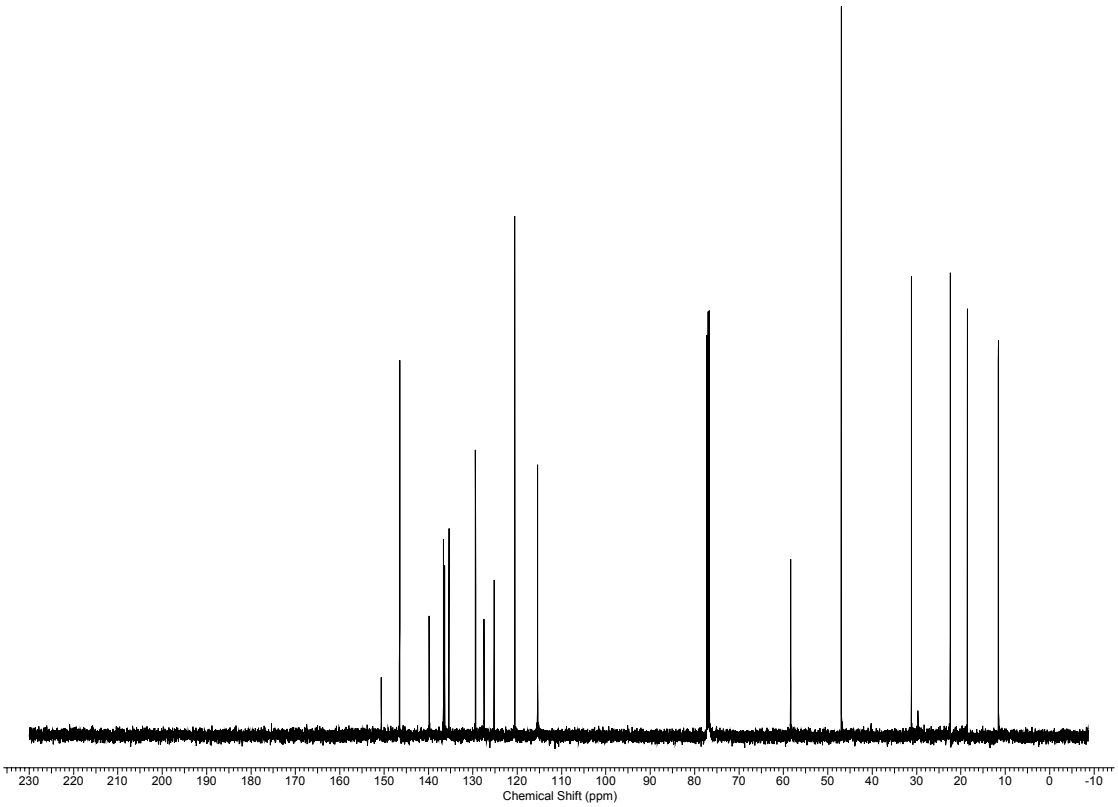
234

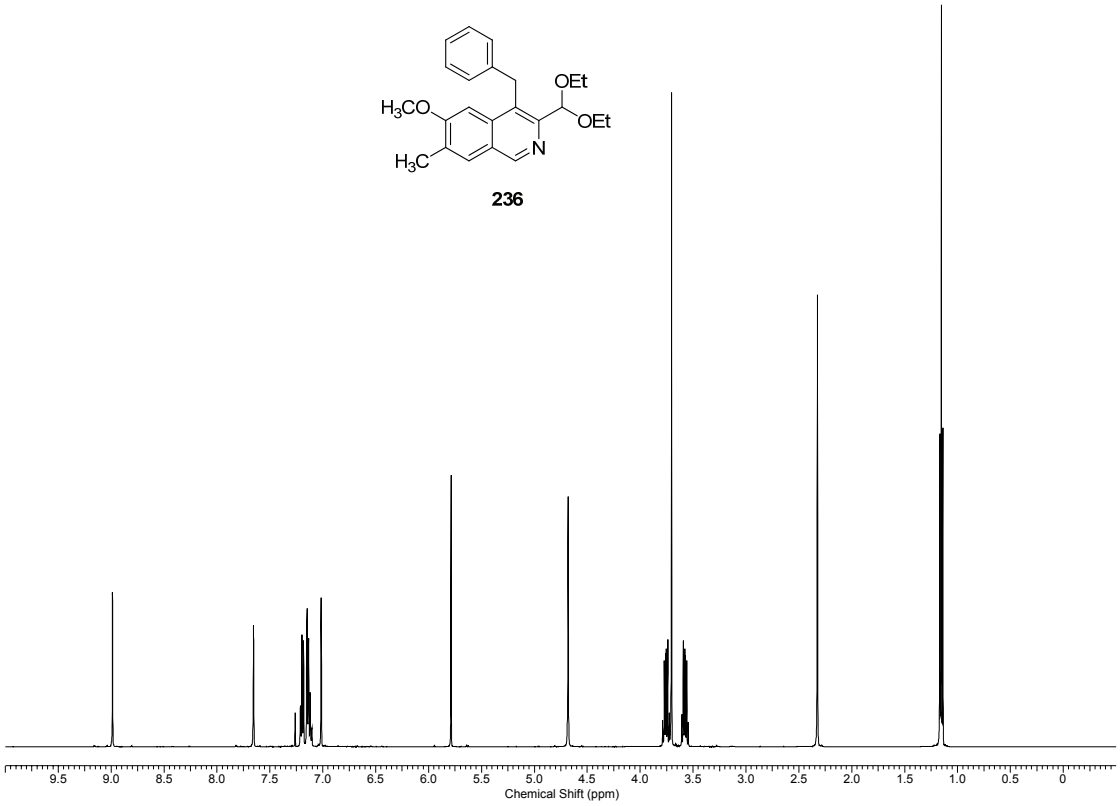

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


H3C
NEt2
N
CH3

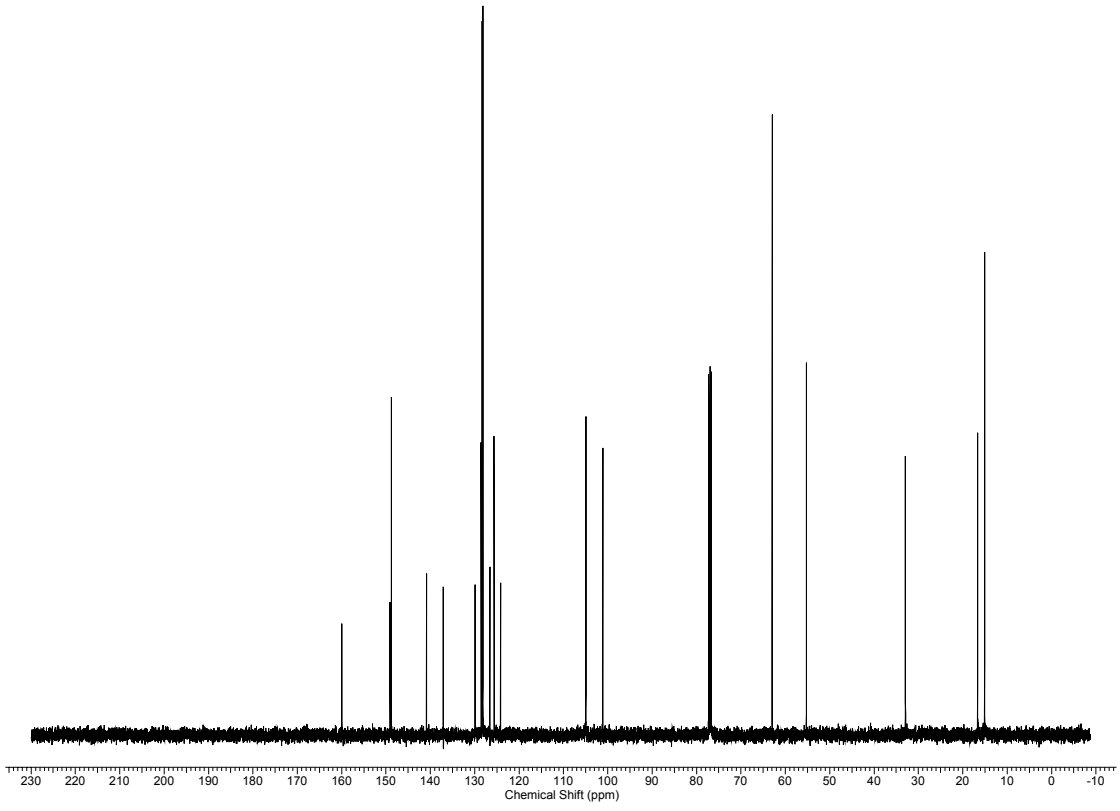
235

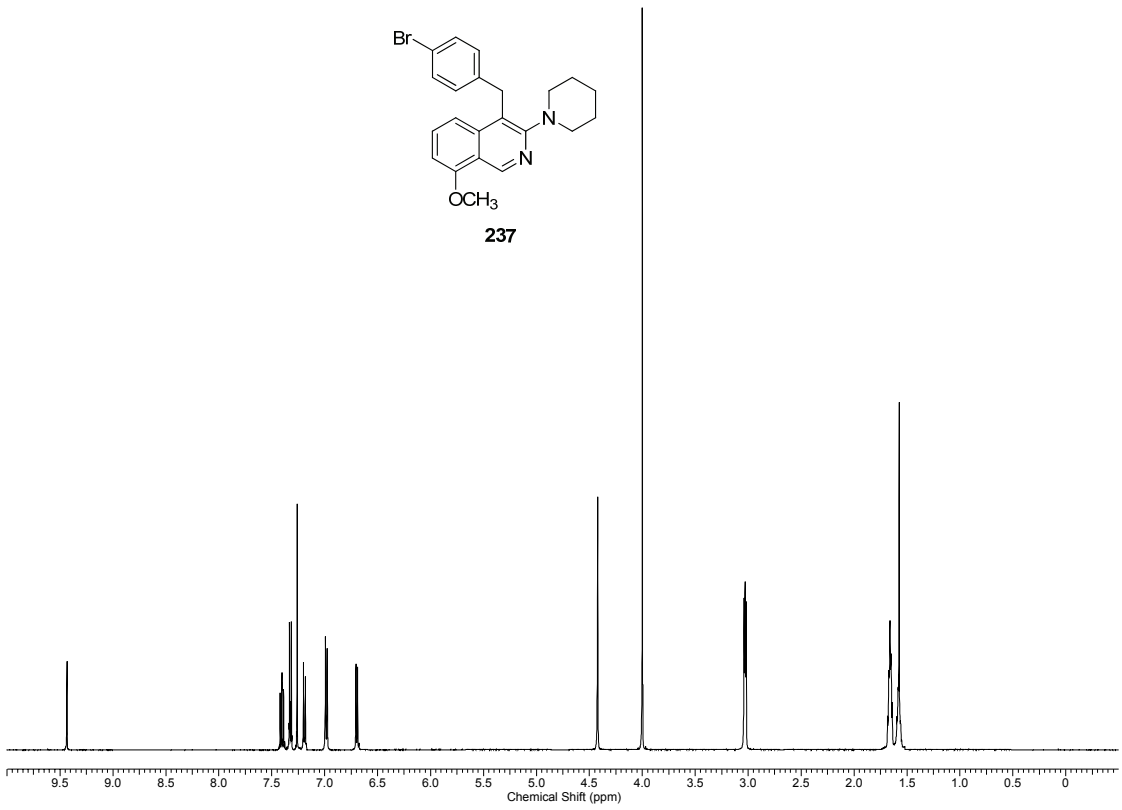

14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
Chemical Shift (ppm)


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

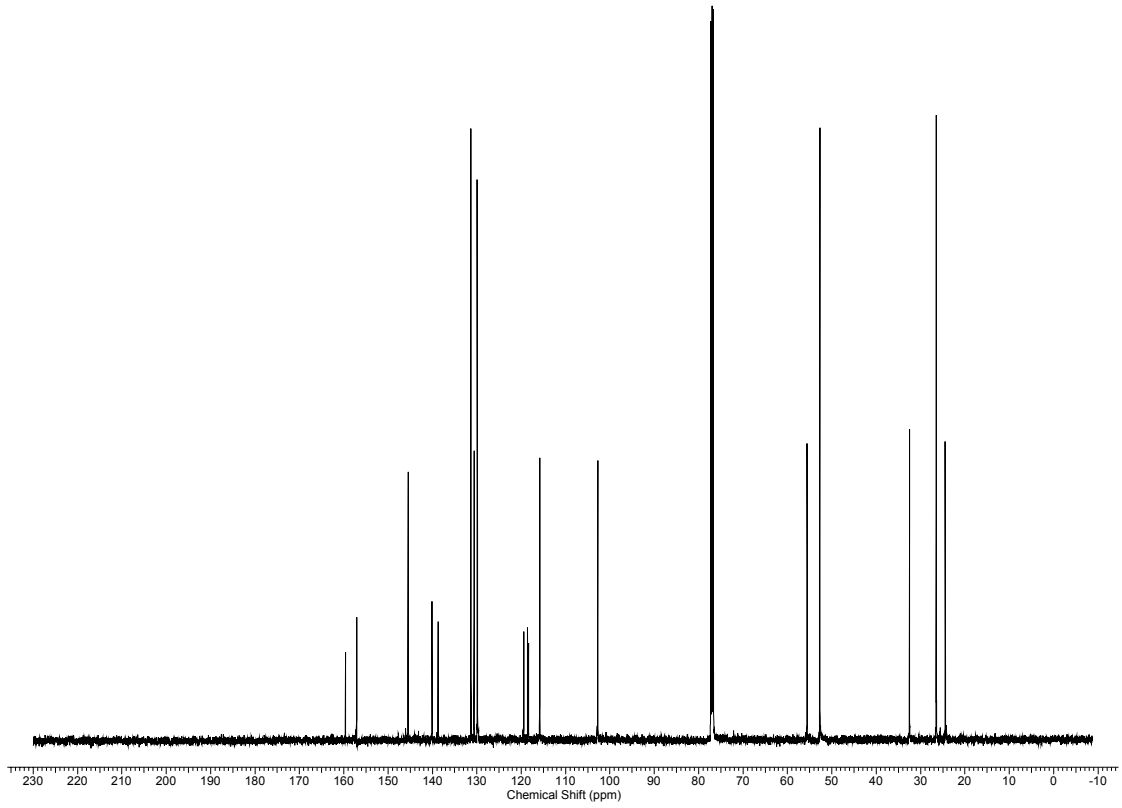

OEt
OEt
H3CO
H3C
N
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

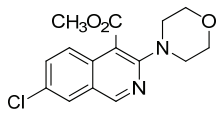
236


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


Br
N
N
OCH3
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

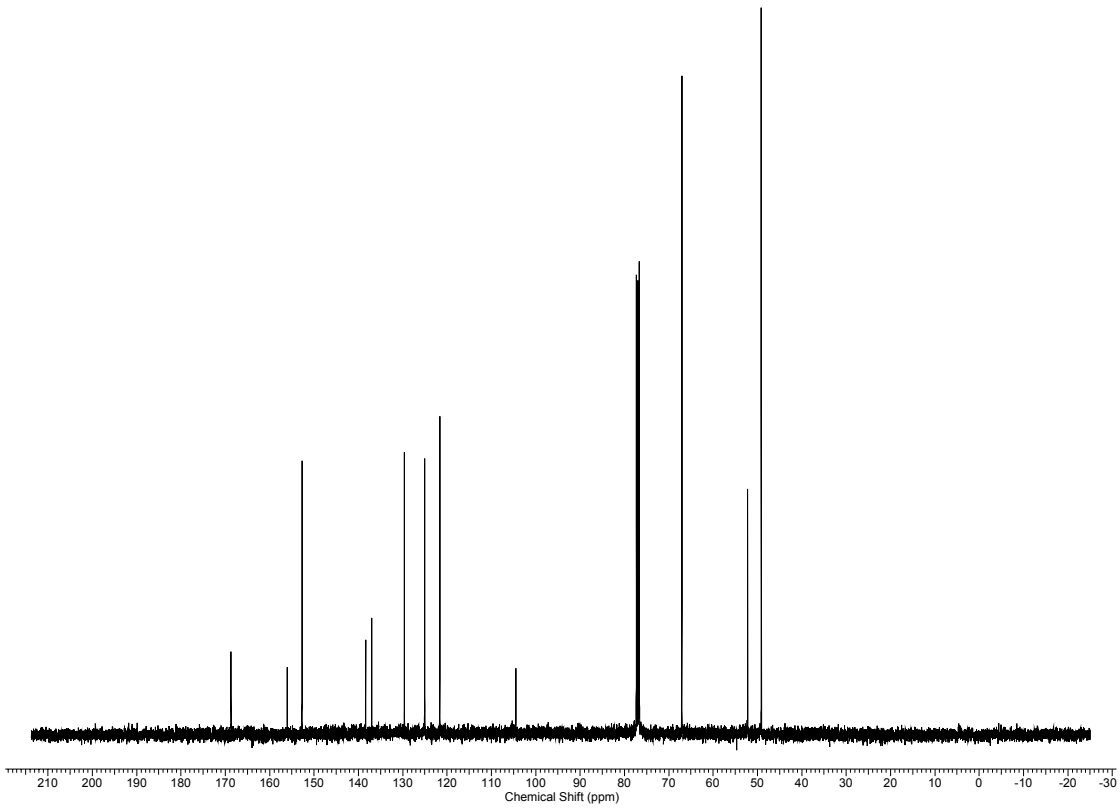
237

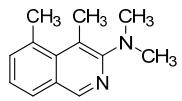

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


CH3O2C
O
N
N
Cl

238

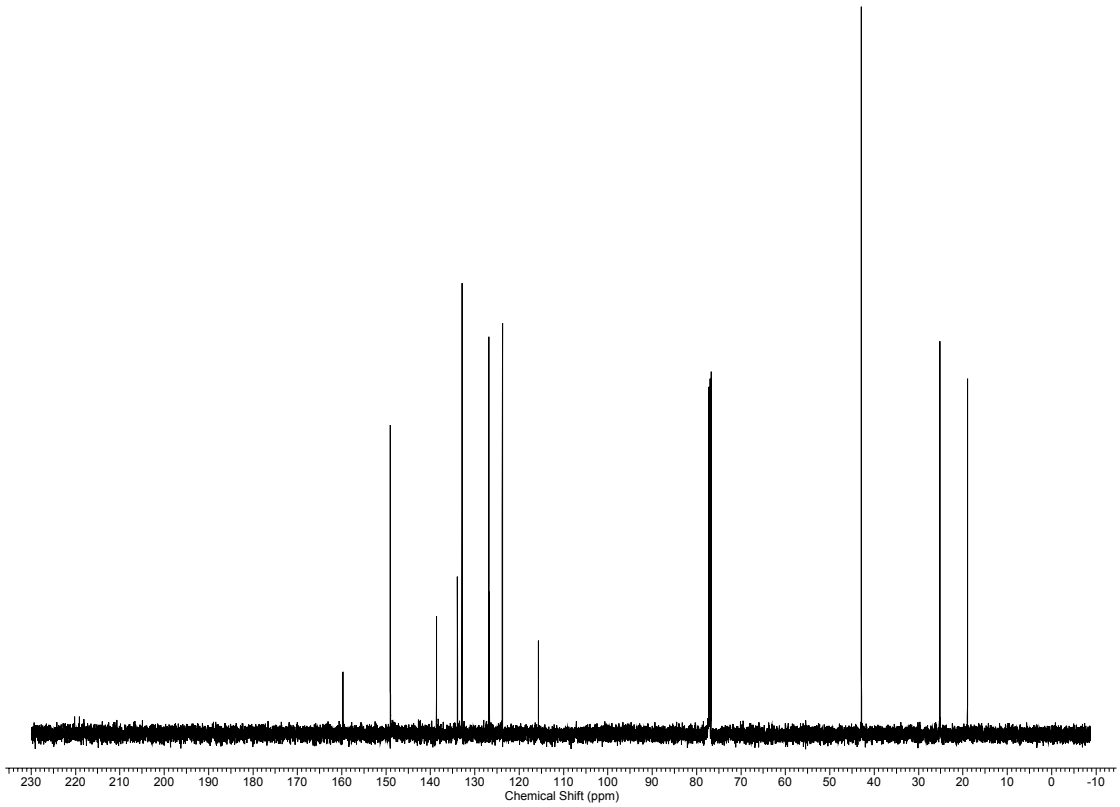
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

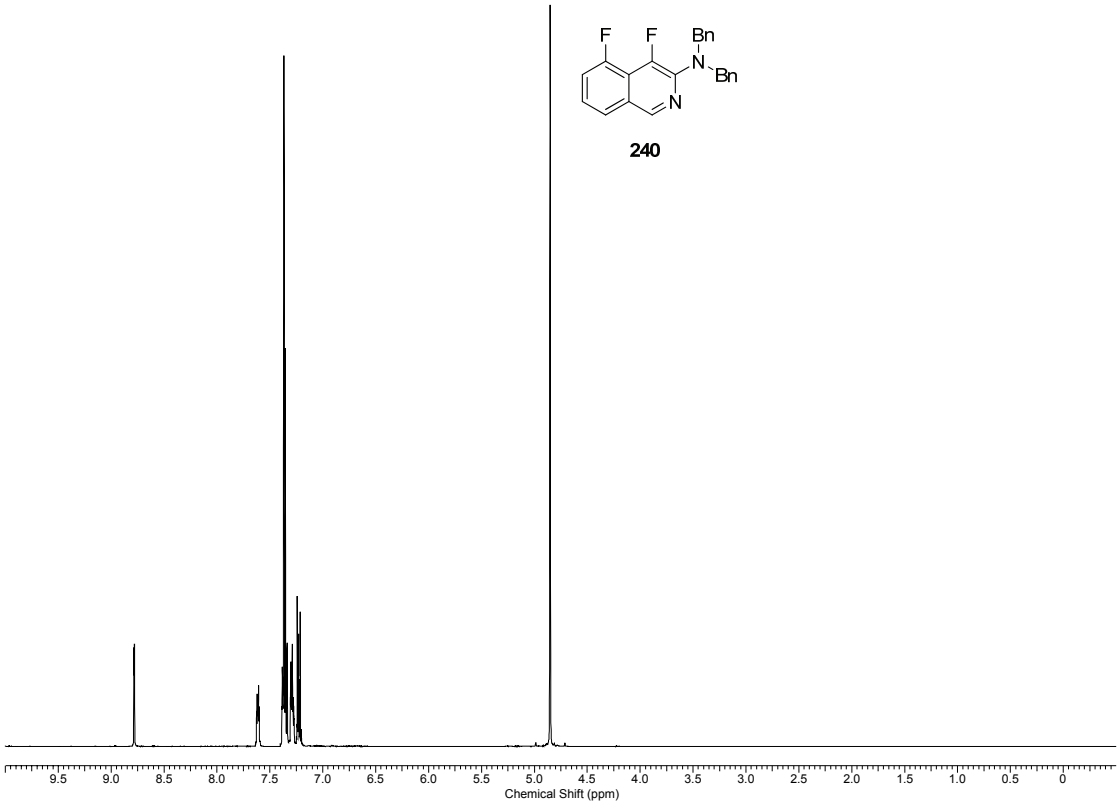

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
Chemical Shift (ppm)

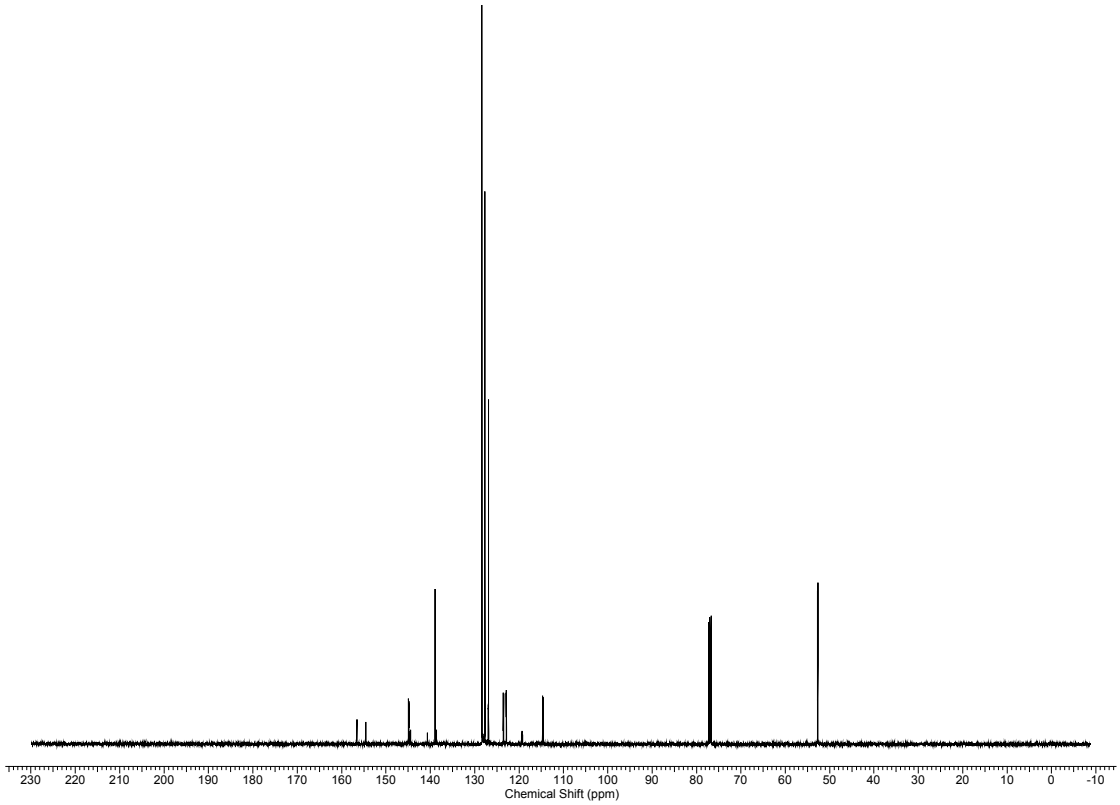


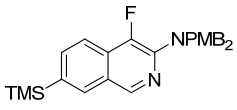
239

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

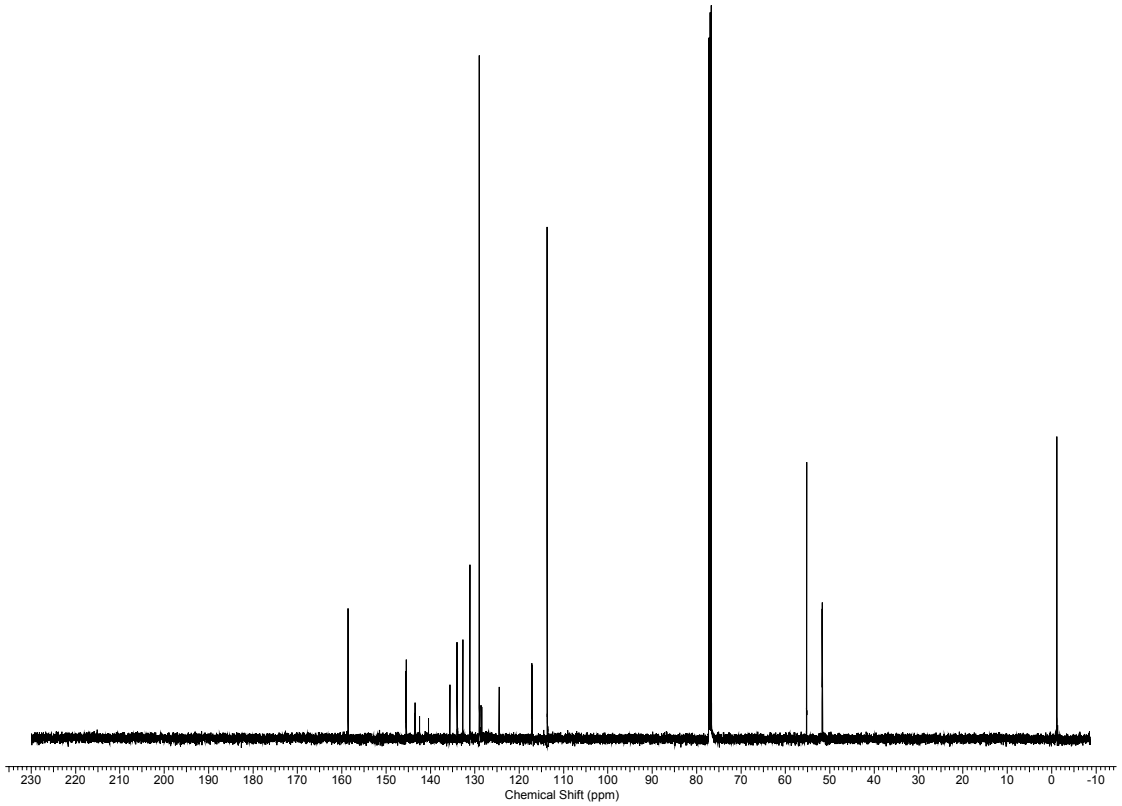

F
F
Bn
N
Bn
N
240
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

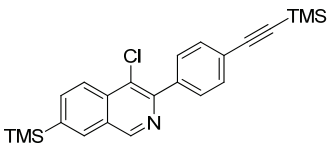

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


F
NPMB2
N
TMS

209

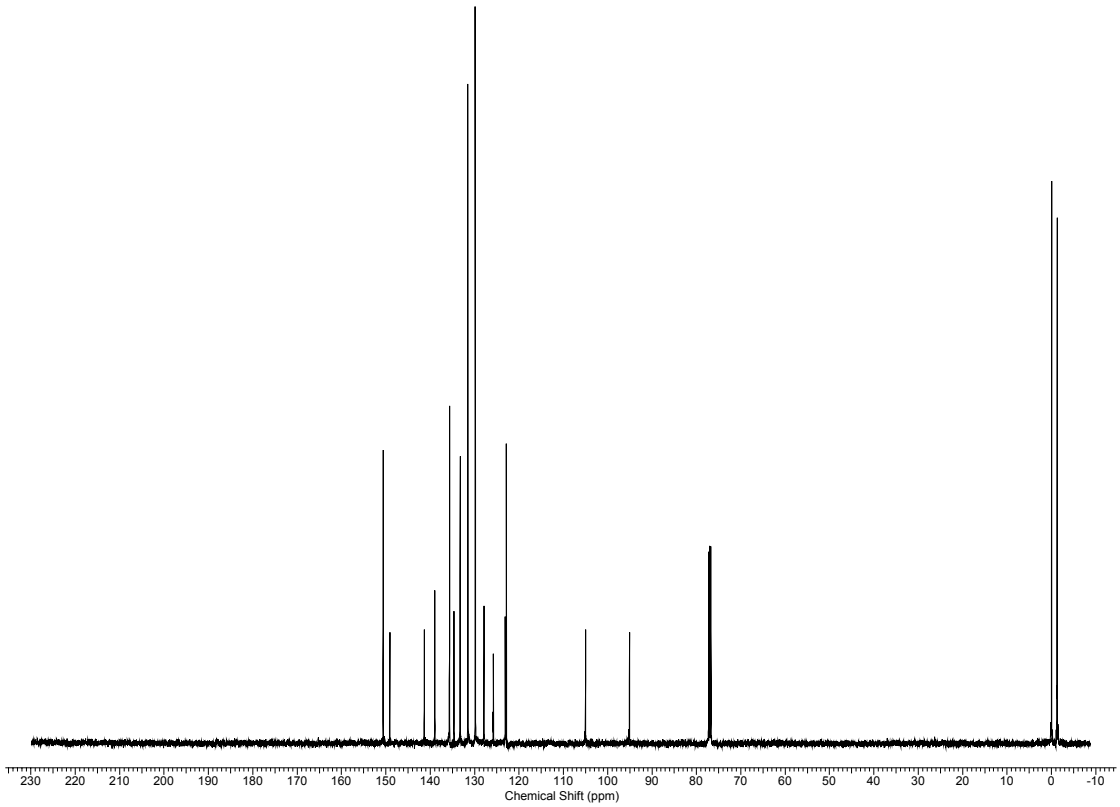
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

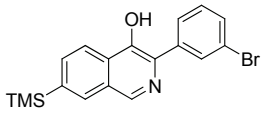

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


TMS
Cl
N
TMS

241

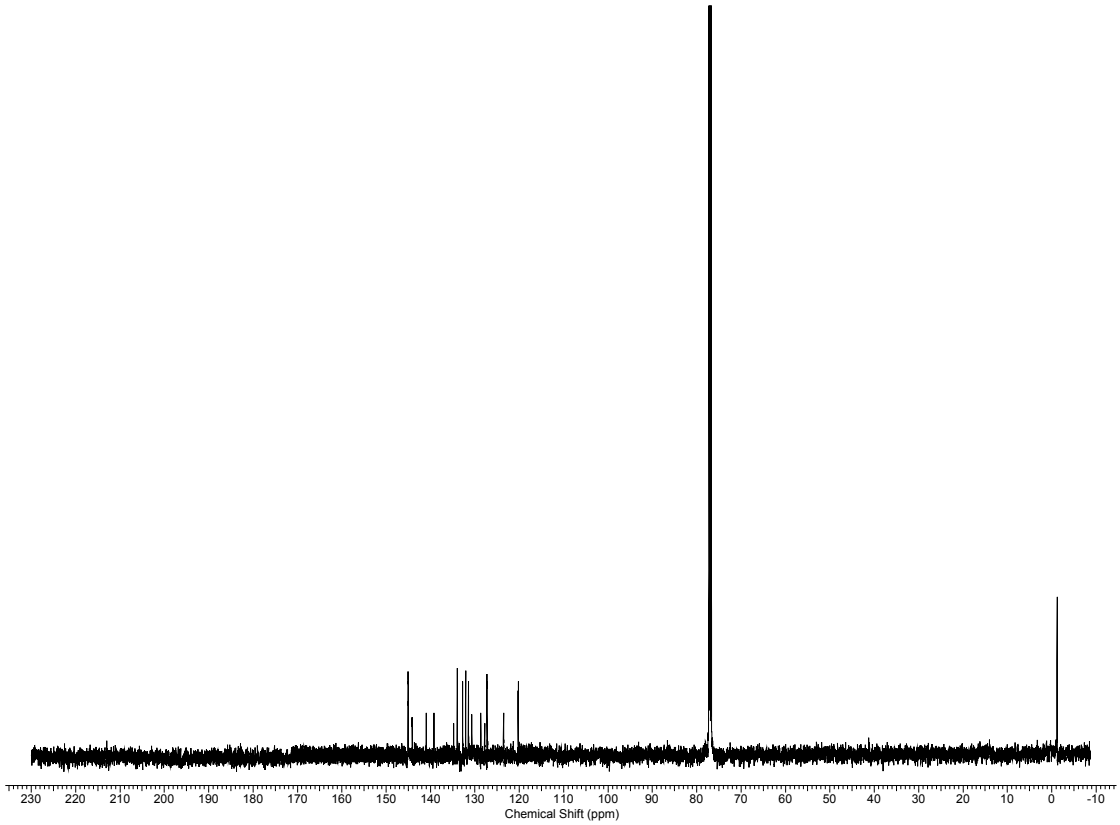
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

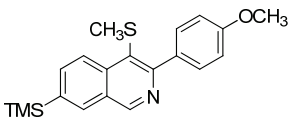

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


OH
Br
N
TMS

242

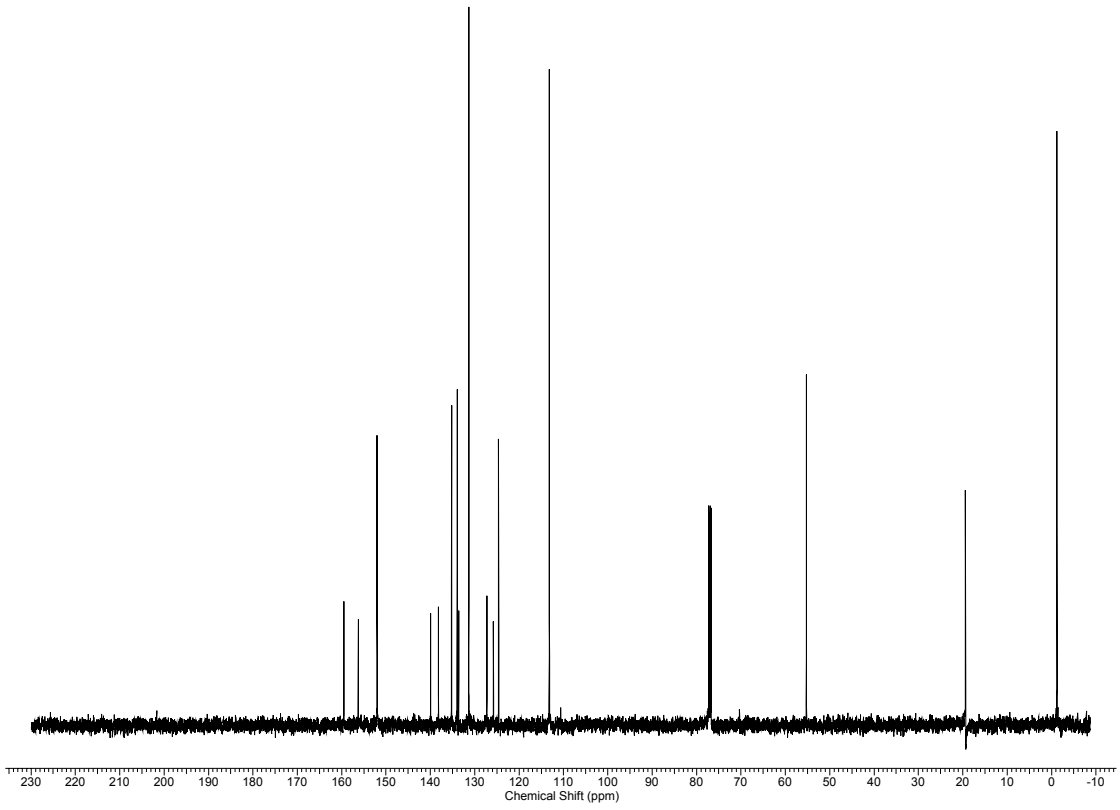
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

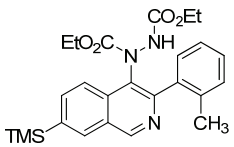

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


CH3S
OCH3
N
TMS

243

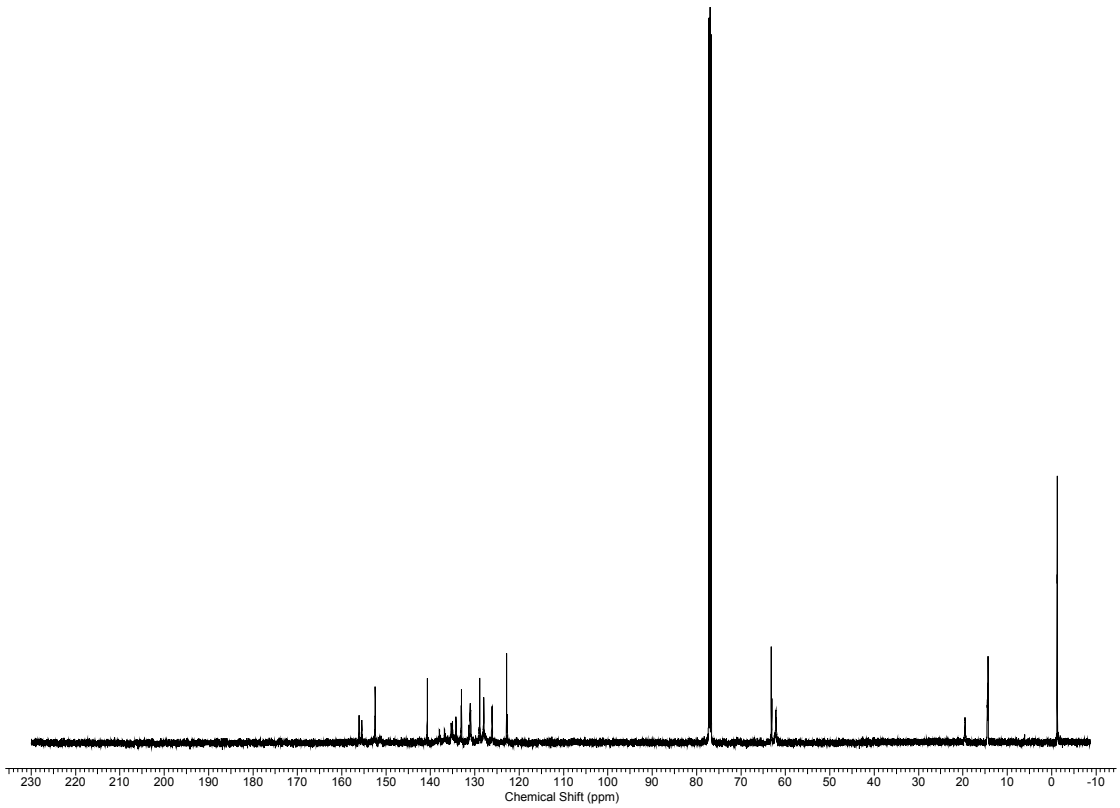
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

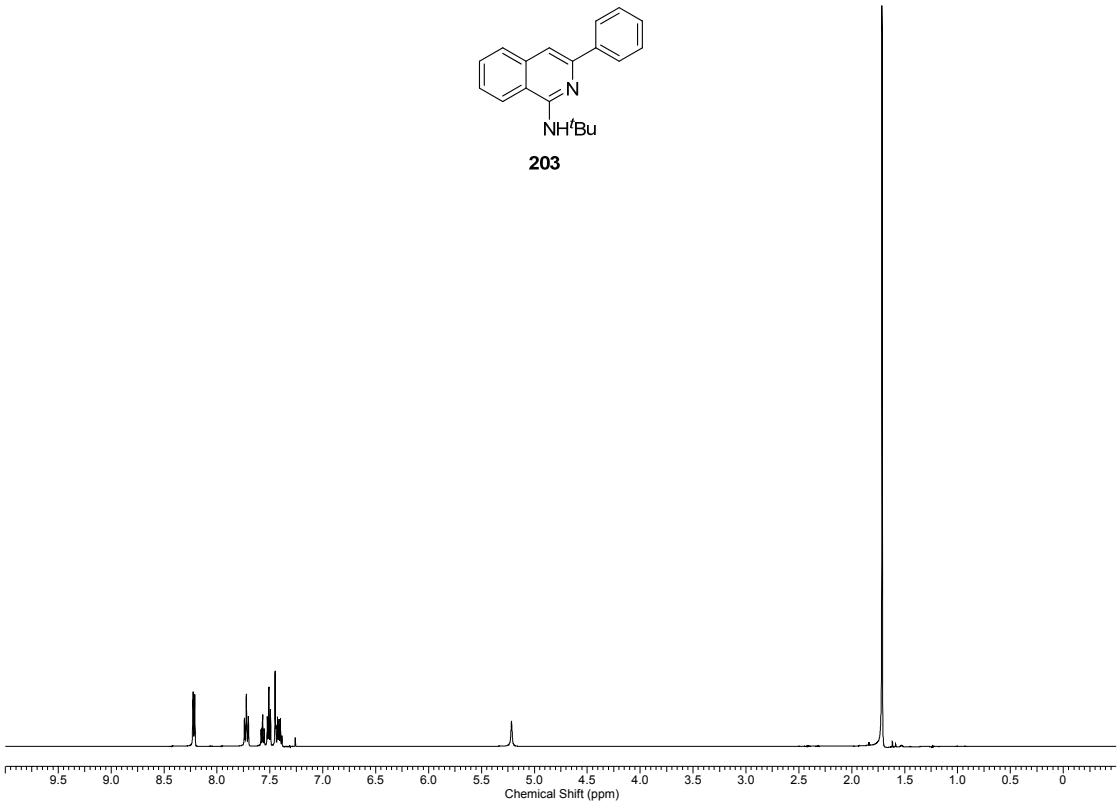

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


CO2Et
EtO2C
N
NH
TMS
N
CH3

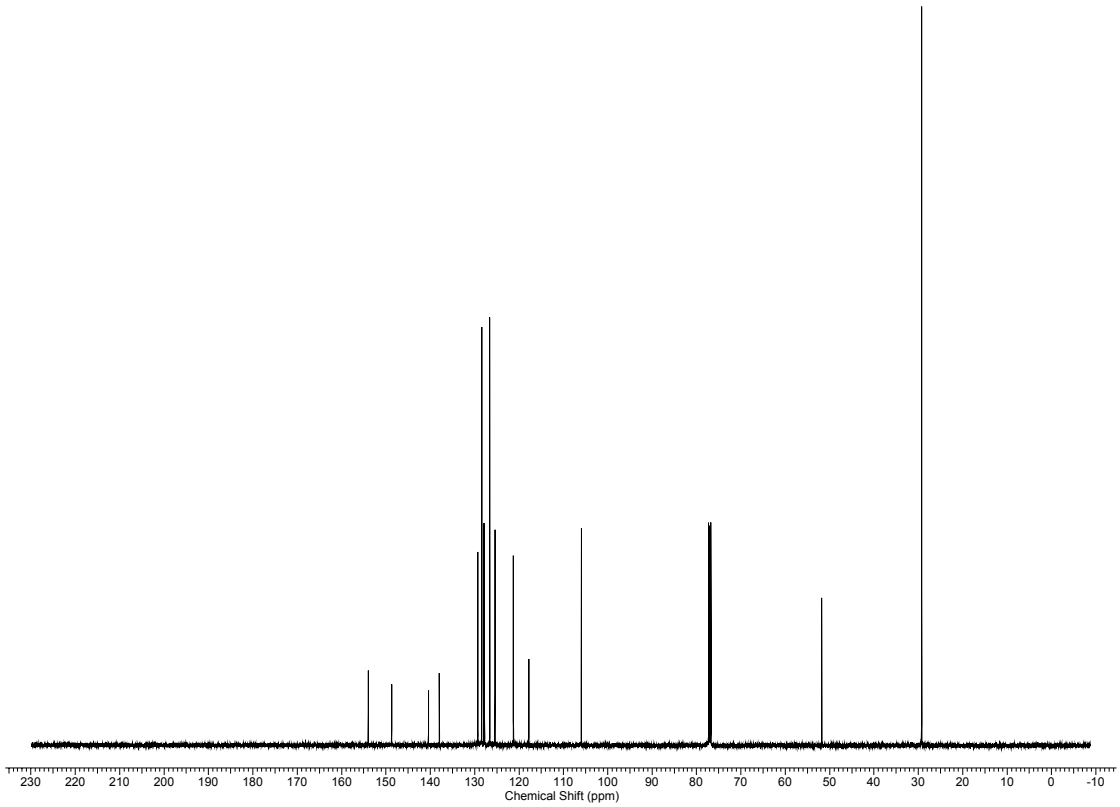
244

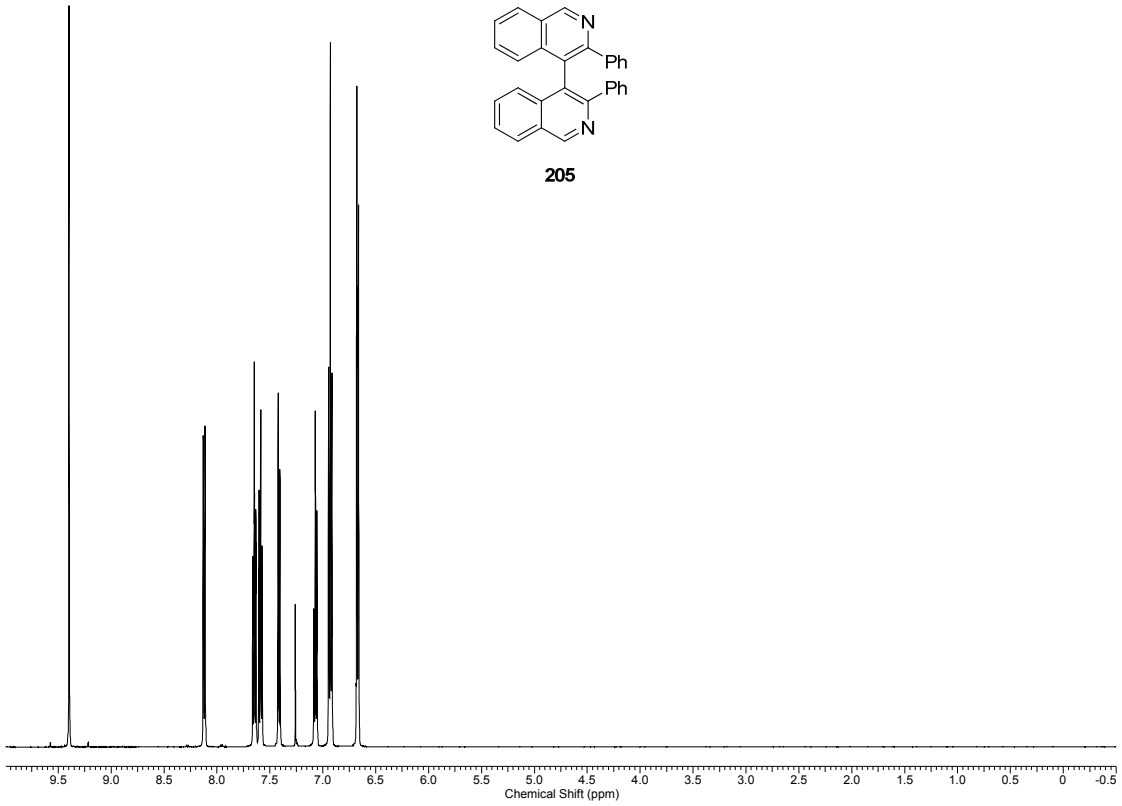
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)

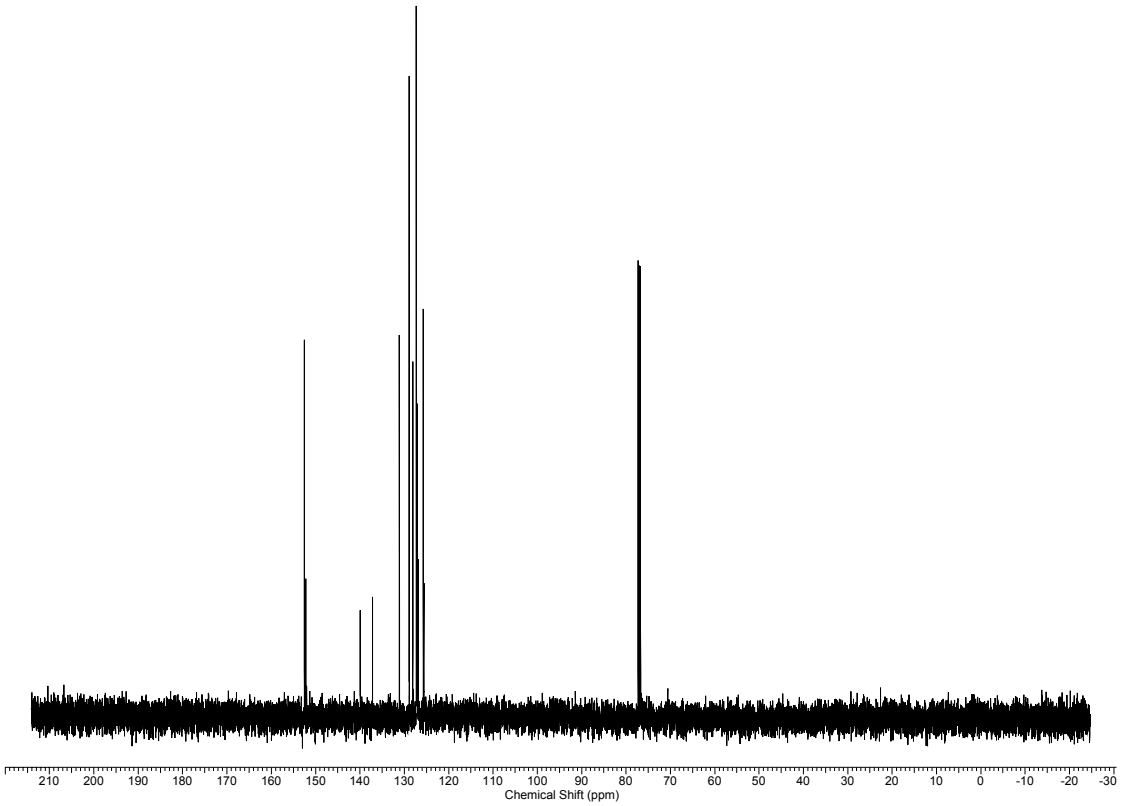

N
NH^{t}Bu
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

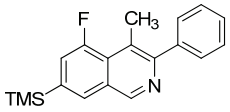
203


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


N
Ph
Ph
N
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0 -0.5
Chemical Shift (ppm)

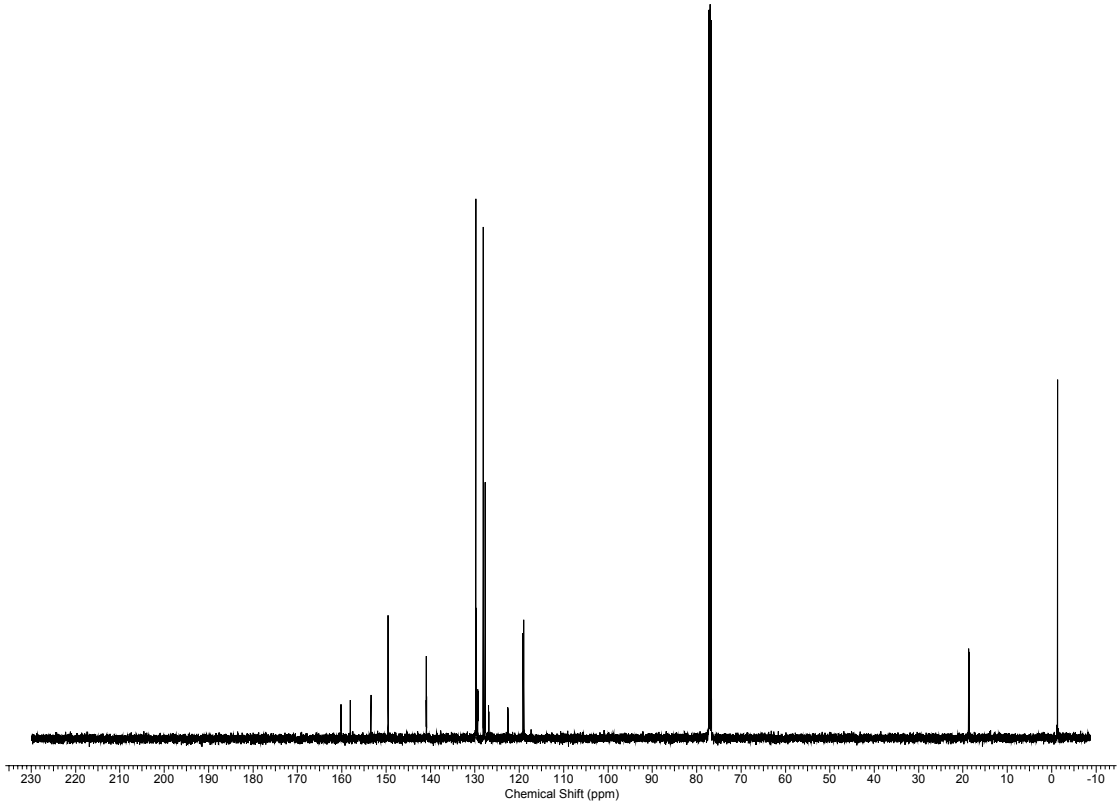
205

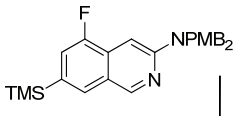

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
Chemical Shift (ppm)


F
CH3
TMS
N

207

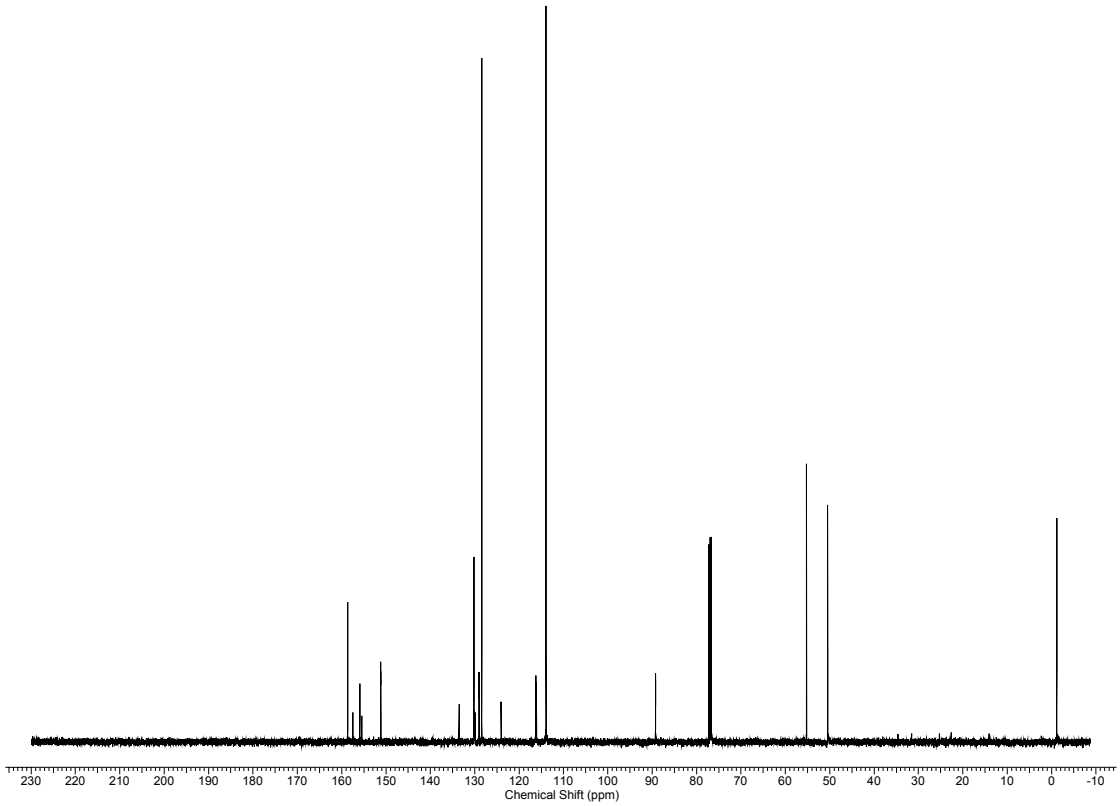
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

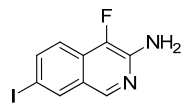

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


F
NPMB2
N
TMS

208

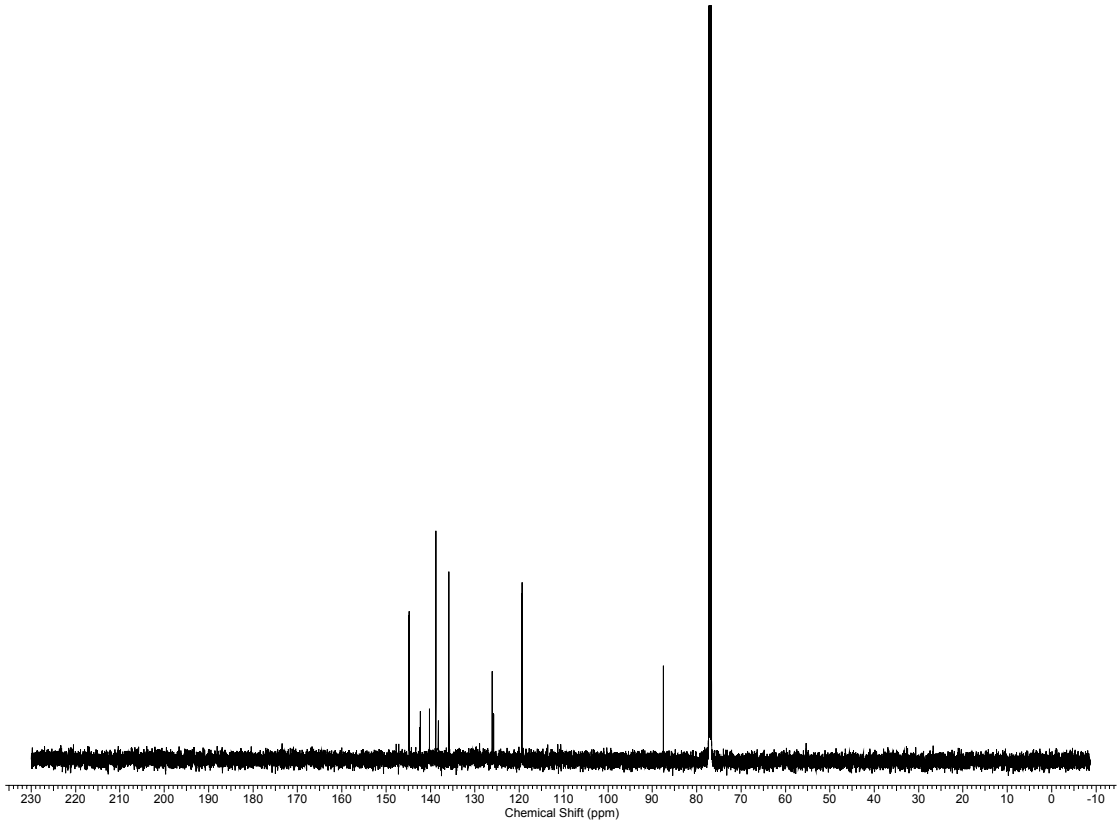
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

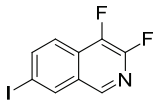

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


F
NH2
N
I

210

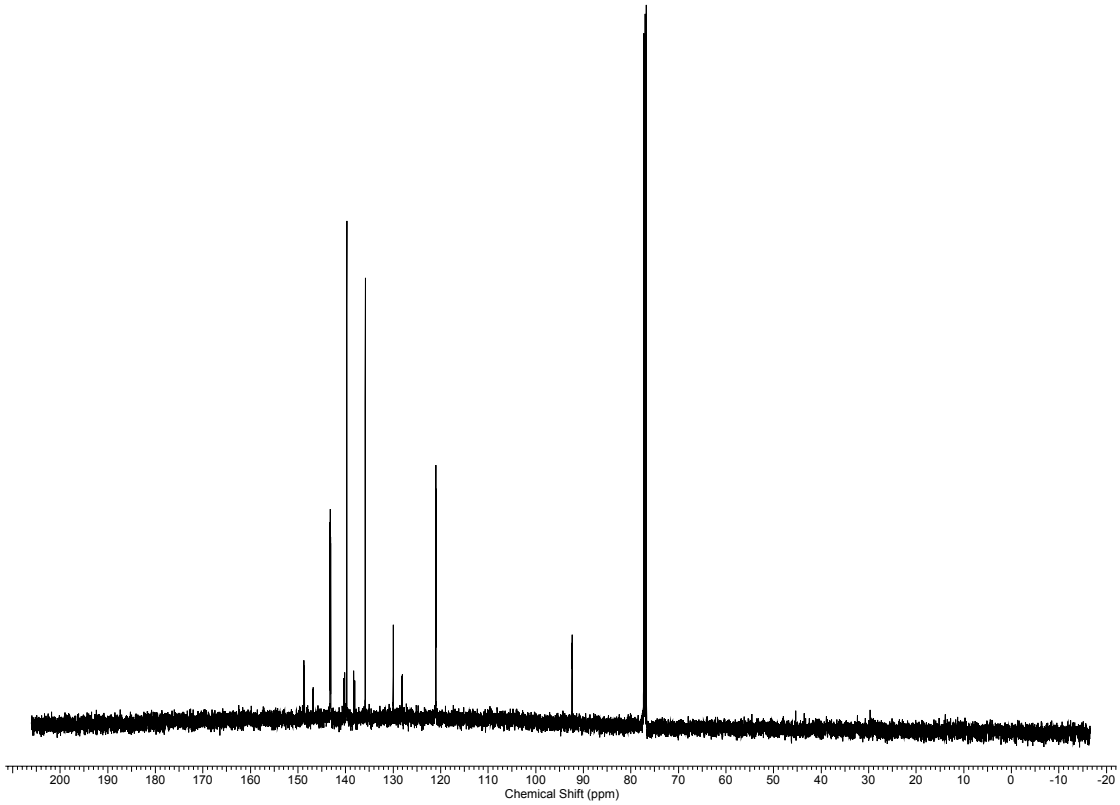
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


F
F
N
I

211

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)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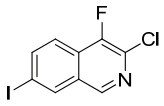
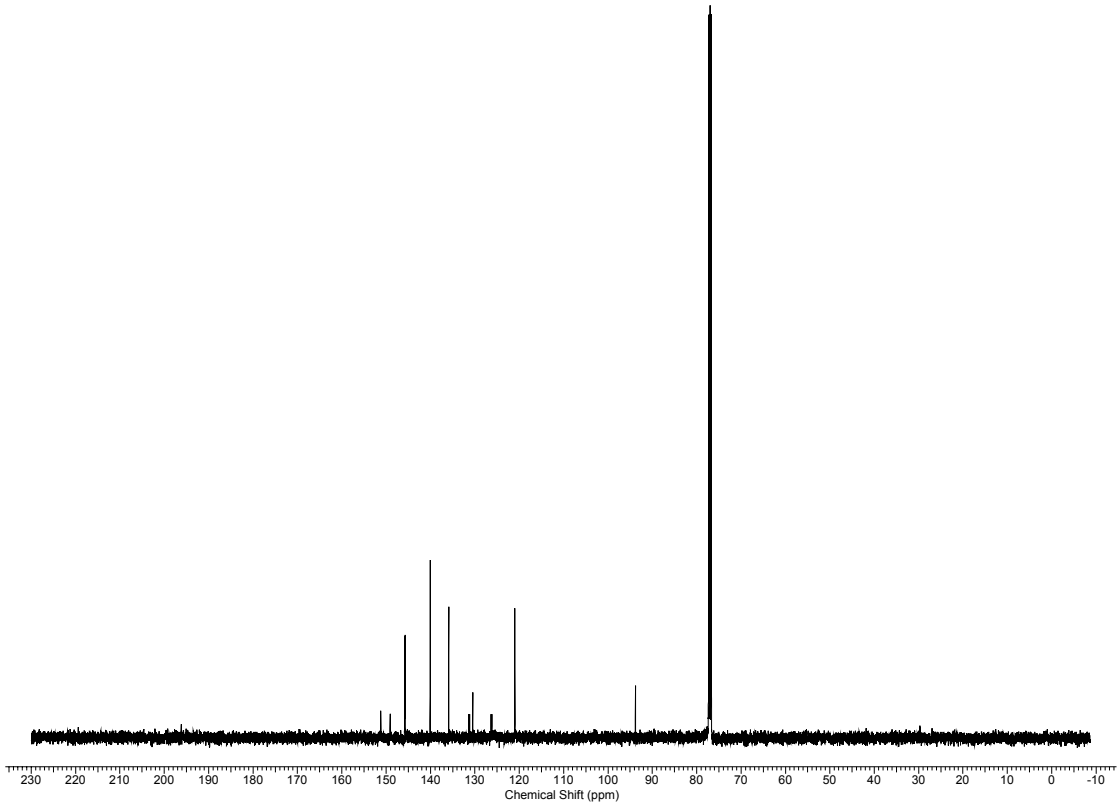
Chemical Shift (ppm)


F
Cl
N
I

212

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)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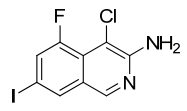
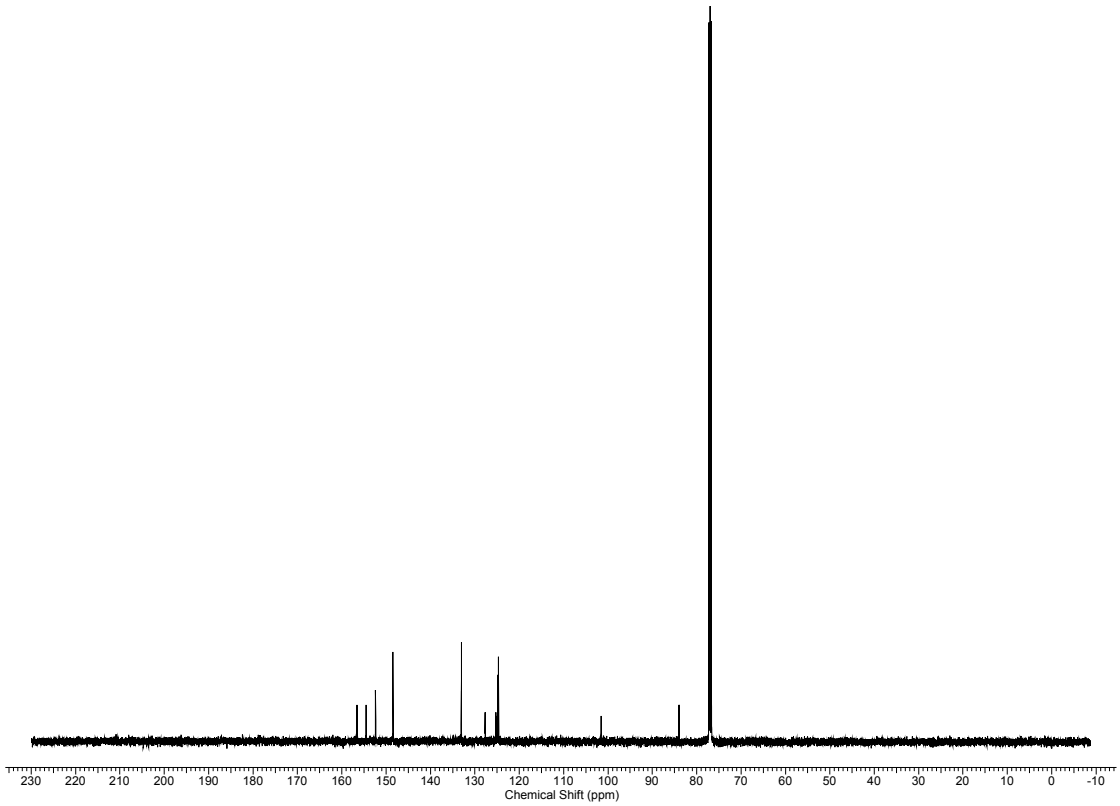
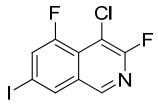
Chemical Shift (ppm)


F
Cl
NH2
N
I

213

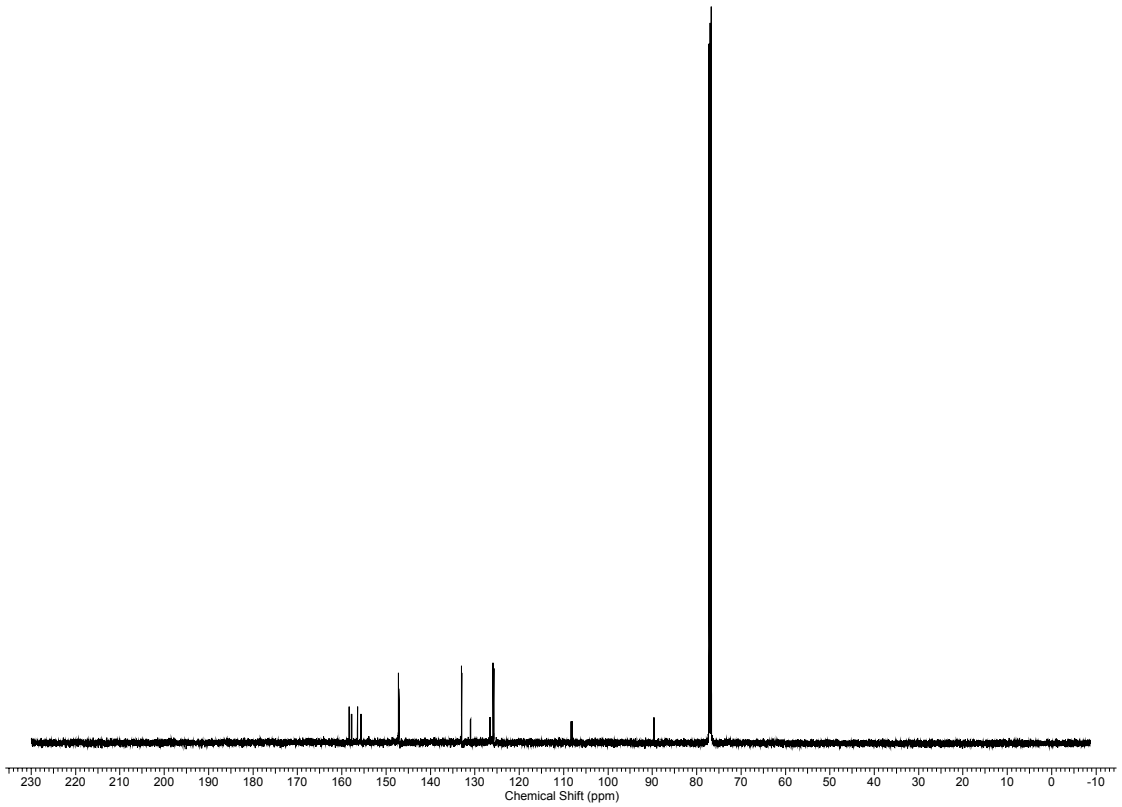
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

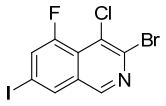

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


F
Cl
F
I
N

214

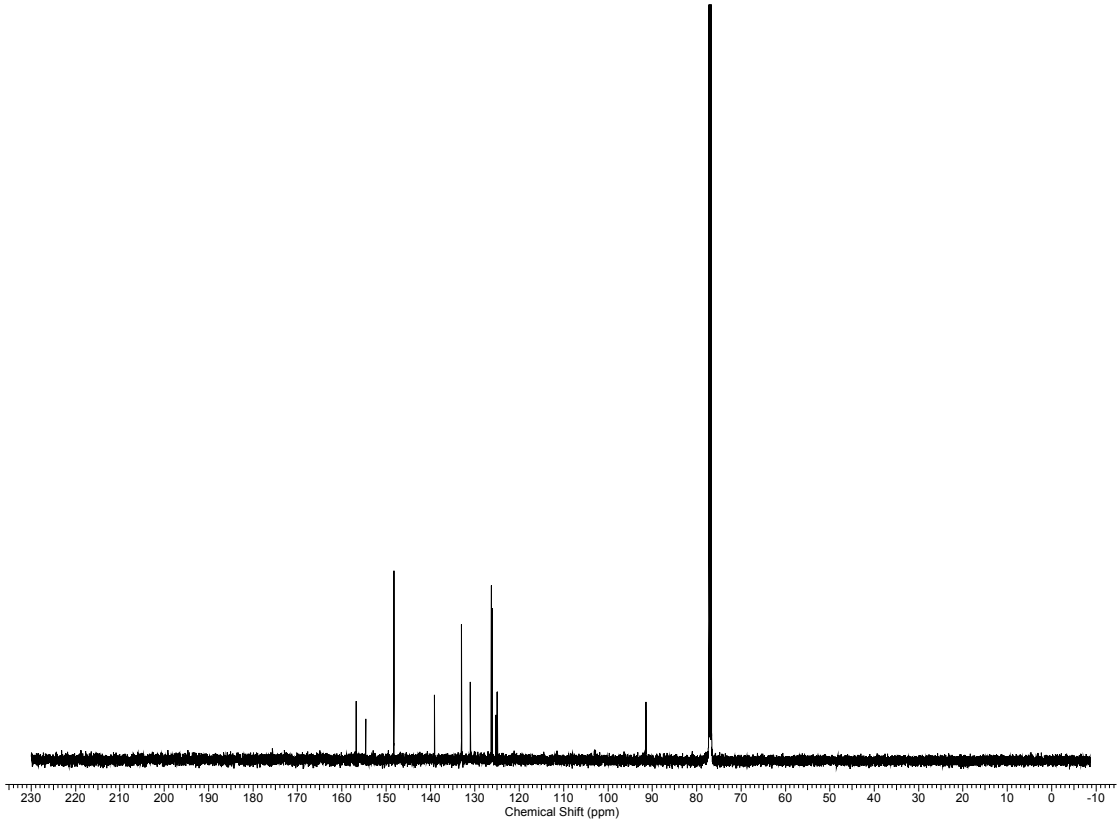
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)

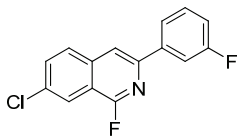

230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


F
Cl
Br
N
I

215

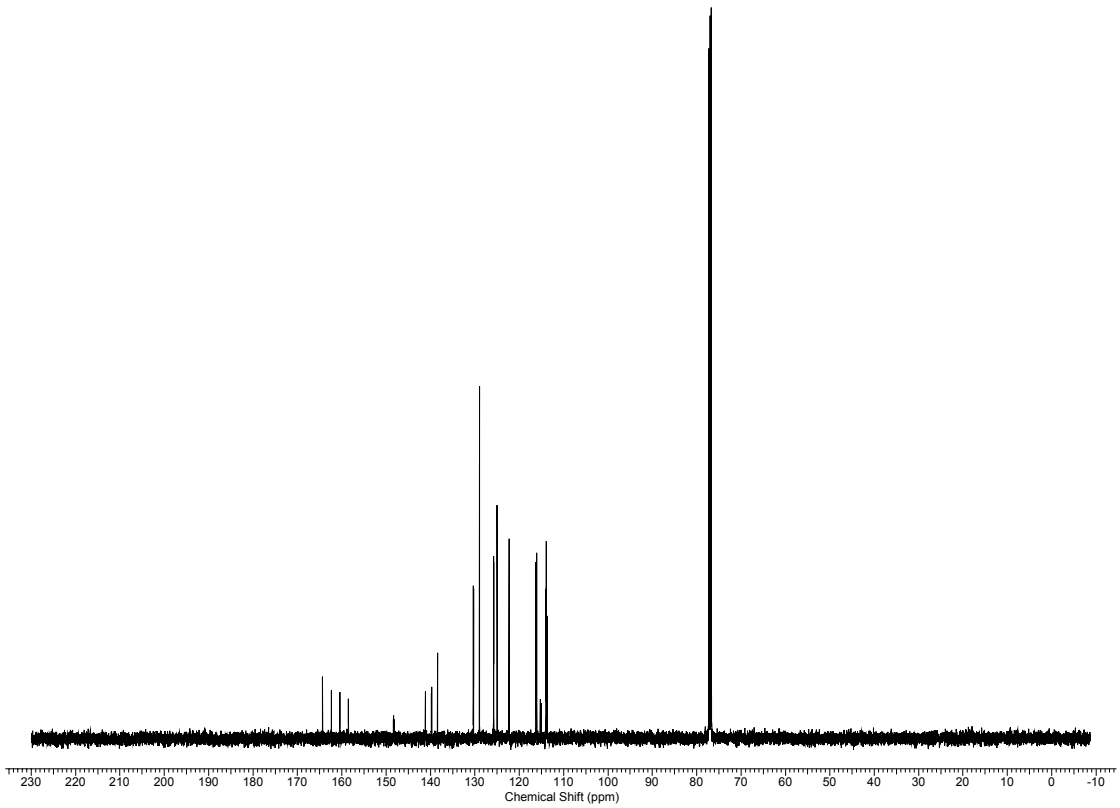
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)


Cl
N
F
F

218

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
Chemical Shift (ppm)


230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
Chemical Shift (ppm)