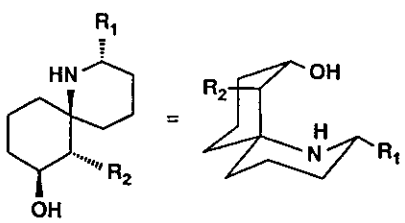
A ROUTE TO 1-AZASPIRANS RELATED TO PERHYDROHISTRIONICOTOXIN

Charles M. Thompson

Dept. of Chemistry, Loyola University of Chicago, Chicago, Illinois 60626, U.S.A.

Abstract- Described herein is a brief synthetic approach to 1-azaspirans. The key transformations in the sequence, starting from 2-cyclohexenone, employ a chelation-assisted regiochemical ring opening of an epoxide and the Lewis acid promoted, bis-homoenolate dianion addition to a [substituted] cyclohexyl-N-benzylimine.

Histrionicotoxin (HTX; **1a**), a substance isolated from the skins of the "arrow poison frog" *Dendrobates histrionicus* and its congeners, perhydrohistrionicotoxin (**1b**) and depentylhistrionicotoxin (**1c**) have been the subject of considerable synthetic[1] and biological[2] interest. The unique 1-azaspiro[5.5]undecane ring system combines with a strict stereochemical orientation of cyclohexyl substituents to pose a formidable synthetic challenge. Biological interest in **1a-c** arises from the fact that these molecules block post-synaptic membrane depolarization without interfering with acetylcholine binding. Hence, these materials are important biochemical tools to study the mechanism of action of cholinergic agonists. Since a source of the natural material is limited, it is of interest to develop synthetic approaches to these and related compounds. Further, owing to the unique spatial arrangement of amino and hydroxyl moieties conferred by the azaspirocyclic skeleton, routes to novel, ring-substituted analogs that affect this specific arrangement could aid our understanding of the receptor requirements.



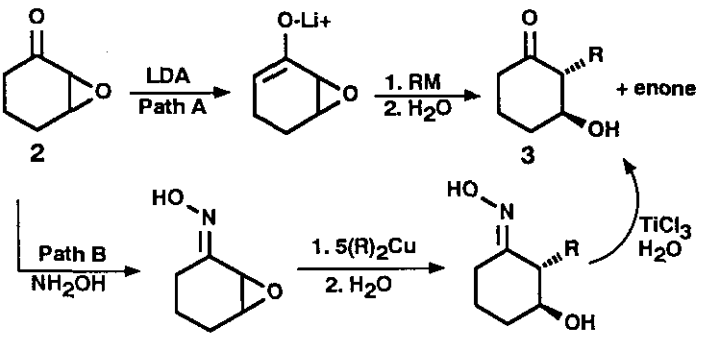
1a: Histrionicotoxin: R_1=CH_2CH=CH-C≡CH
R_2=CH=CH-C≡CH

1b: Perhydrohistrionicotoxin: R_1= n-C_5H_{11}
R_2= n-C_4H_9

1c: Depentylhistrionicotoxin: R_1=H
R_2= n-C_4H_9

Previously, we reported the synthesis of 2-piperidones *via* the addition of the "remote" (bis-homoenolate) dianion of 4-phenylsulfonylbutanoic acid (4-PSBA) to various activated imines.[3] Extension of this method to the histrionicotoxin series requires a *trans*-2-substituted 3-hydroxyl-cyclohexanone with the expectation that conversion to the imine and reaction with the dianion of 4-PSBA would afford an azaspirocycle viable for further elaboration.

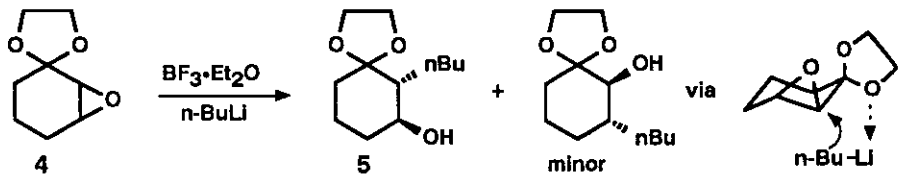
Surprisingly, there were few methods reported for the reliable preparation of 2-alkyl-3-hydroxy-cyclohexanones. Two noteworthy examples use 2,3-epoxycyclohexanone (**2**) as a starting material to prepare 2-butyl-3-hydroxycyclohexanone (**3**), a valuable precursor for the synthesis of **1b** and **1c**, *via* carbanion chemistry (path A)[4] or via oximes (path B).[5] However, as cited by one of the authors,[5] dehydration to the enone may accompany the isolation of **3**. This side reaction also surfaced during our scale up procedures.



As a result we sought alternative methods for the preparation of this relatively simple, substituted cyclohexane system. A prior report by Ganem[6] showed that organolithium additions to epoxides may be enhanced by boron trifluoride etherate. We intended to utilize this reaction in the construction of an intermediate that would not dehydrate and concentrated our effort upon the preparation of the cyclic ketal derivative (**5**), which suitably protected, would serve as a stable precursor for a synthesis of **1b** and **1c**. Thus, the ketal (**4**) (76% from cyclohexenone: a. TsOH, $HOCH_2CH_2OH$, toluene, $-H_2O$, 4 h, b. m-CPBA, 1.3 eq., $NaHCO_3/CH_2Cl_2$, 24 h) when treated sequentially with boron trifluoride etherate (1 eq.) and n-BuLi (1.5 eq.) at -78 °C in THF, resulted in an 80% yield of the 2-butyl regioisomer (**5**) (Scheme 1). The regiochemistry was confirmed by

^{1}H nmr (doublet of triplets for C_3-H) and comparison to authentic (**3**),[4] prepared by mild removal of the ketal (10% HCl, dioxane, room temperature). The predominant production of the desired 2-alkyl regioisomer may arise, in part, from chelation of the organometallic to the ketal oxygens.[7]

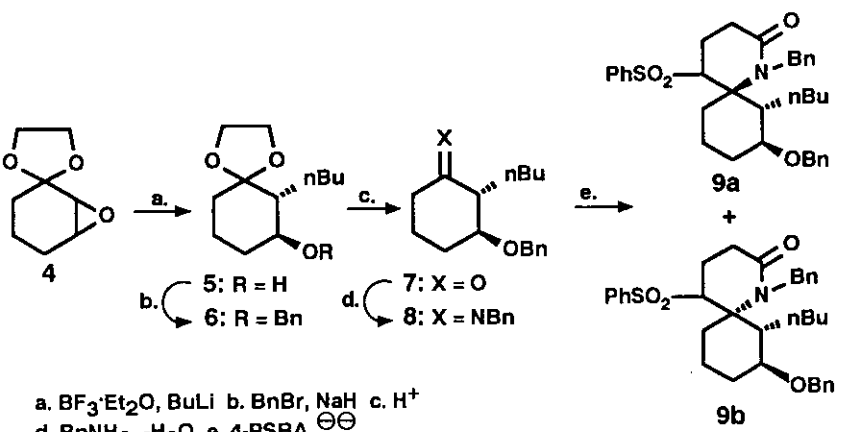
Scheme 1



We also have found that PhLi and sec-BuLi add to the activated epoxide (**4**) in similar regioselectivity and yield. t-Butyllithium reacts preferentially at the 2-position but a lower yield was obtained. Further research activity in this area is currently underway.[8]

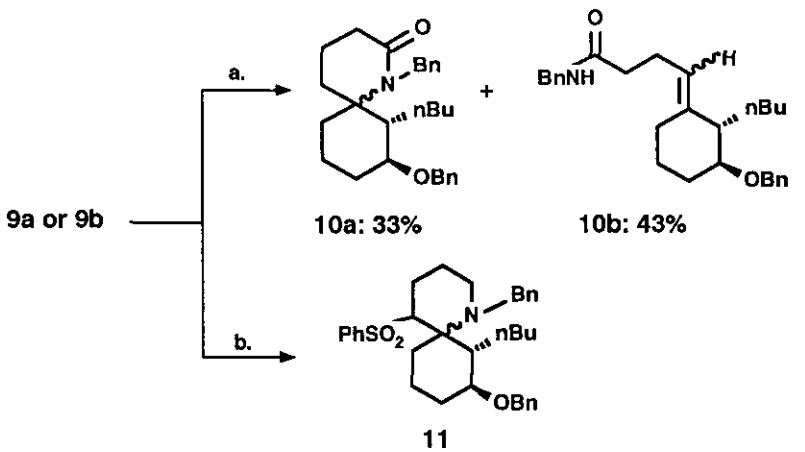
Alcohol (**5**) was protected as the benzyl ether (**6**) and the ketal removed to afford the desired 2,3-disubstituted cyclohexanone (**7**) in 79% overall yield. Quantitative conversion to the imine (**8**) was accomplished by reaction with benzylamine *via* azeotropic removal of water. Reaction of the imine, activated by boron trifluoride etherate, with the dianion of 4-PSBA[3] affords the diastereomeric 1-azaspirans (**9a/9b** (7:3 ratio)) in 85% yield (Scheme 2). The stereochemistry at the spirocyclic ring center and C-5 have not yet been established.

Scheme 2



With the 1-azaspiran system established, some preliminary investigations exploring the defoliation of the 2-piperidone ring were initiated (Scheme 3). Reductive cleavage of the phenylsulfone moiety (Na-Hg), afforded **10a**, however, the reaction was accompanied by the alkene-elimination product (**10b**). We sought to avoid this side reaction by reduction of the lactam carbonyl (BH_3•THF or LAH) to afford piperidine (**11**),[8] followed by removal of phenylsulfone group. However, this alternative strategy also showed that a retro-Michael reaction may predominate during the carbonyl reduction to afford a vinylsulfone, though cautious addition of reagent suppresses this problem.

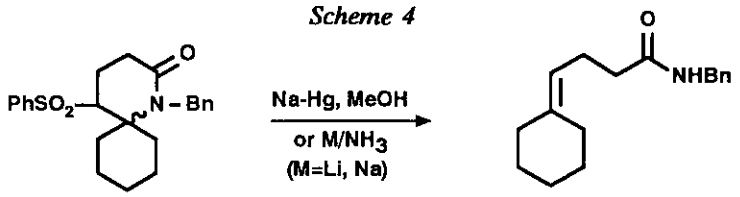
Scheme 3



Other sulfone-cleavage procedures[9] were examined including Li/NH_3 and Na/NH_3 that also showed **10b** to be the major product along with **10a** and O-debenzylated material. As a further check of this desulfonylation, eliminative pathway, we subjected an unsubstituted, model azaspirocycle (**12**)[3a] to the same reductive cleavage conditions and found again that an elimination product (**13**) dominated (Scheme 4). Studies toward the total synthesis of perhydrohistrionicotoxin will therefore require a more thorough future investigation.

In conclusion, a rapid and versatile approach to the 5-phenylsulfonyl, 1-azaspiran ring system of perhydrohistrionicotoxin incorporating remote dianion methodology as the key step has been

Scheme 4



12 13

achieved. Some advantages of this approach are the brevity (7 steps from 2-cyclohexenone), a new path to intermediate (7), and stereochemical control over the carbon-ring substituents. With the regiochemistry of the substituents established, an nmr investigation is underway to establish the role of the phenylsulfone moiety upon the conformation of these azaspirans.

EXPERIMENTAL

Melting points were determined using a Mel-Temp melting point apparatus and are uncorrected. ^{1}H nmr spectra were taken in deuterated chloroform ($CDCl_3$) at either 60 or 300 MHz. Coupling constants (J) are in hertz (Hz). ^{13}C Nmr was conducted at 75 MHz and peaks are relative to the deuterated chloroform triplet (δ=77.06). Elemental analyses were conducted at Midwest Microlab, Indianapolis, IN. High resolution mass spectral determinations were conducted at Northwestern University, Evanston, IL. Analytical thin layer chromatography (tlc) was conducted with aluminum backed silica plates (E. Merck). Visualization was accomplished with an ultraviolet lamp and/or anisaldehyde stain (a 2% solution of o-anisaldehyde in 95:4:1 absolute ethanol-concentrated sulfuric acid-glacial acetic acid) with heating. Flash chromatography[10] was conducted with Kieselgel 60, 230-400 mesh (E. Merck). All solvents and reagents were purified when necessary by standard literature methods and reactions were conducted under a positive argon atmosphere utilizing standard techniques.

1,4-Dioxa-6-n-butyl-7-hydroxyspiro[4.5]decane (5). Boron trifluoride etherate (2.5 ml) was added to a solution of epoxy ketal (4) (1.56 g; 10 mmol) in THF (10 ml) at -78 °C and the solution was

stirred for 0.5 h. n-BuLi (5 ml; 11 mmol; 2.2 M in hexane) was added dropwise over 10 min and the reaction was maintained at -78 ^{0}C for 1.0 h. The reaction was diluted with 30 ml of ether and poured into 100 ml of saturated bicarbonate. The mixture was stirred at room temperature for 10 min, the organic layer was separated and the aqueous layer was extracted twice with 50 ml portions of ether. The organic extracts were combined and washed successively with saturated sodium carbonate, water and brine. The solution was dried over sodium sulfate, filtered and concentrated to afford a clear oil. Flash chromatography affords 80% of the 6-n-butyl regioisomer as an oil (approx. 10% of the 7-n-butyl isomer was present in the crude by nmr). Rf = 0.15 (1:1, petroleum ether:ether). ^{1}H Nmr ($CDCl_3$): δ 0.8 (t, J = 6, 3H), 1.1-1.9 (m, 14H), 3.2 (dt, J = 9 and 5, 1H), 3.9 (s, 4H). ^{13}C Nmr ($CDCl_3$): δ 14.0, 23.0, 28.5, 31.7, 32.4, 32.9, 38.2, 40.7, 42.0, 64.3, 73.5, 108.5.

***trans*-1,4-Dioxa-6-n-butyl-7-benzyloxyspiro[4.5]decane (6).** Hydroxy ketal (5) (1.3 g; 6.0 mmol) was dissolved in 7 ml of DMF under a mild flow of argon. Sodium hydride (0.30 g; 7.5 mmol; 60% suspension) was added in portions over 0.5 h at room temperature. Benzyl bromide (1.0 ml; 8 mmol) was added slowly, and the reaction was warmed to 80 ^{0}C for 2.0 h. The oil bath was removed, the reaction mixture was cooled to room temperature and diluted with 100 ml of ether-isopropanol (99:1). The organic layer was washed thrice with 50 ml portions of water and once with brine. The organic layer was dried over sodium sulfate, filtered and concentrated to an oil. Flash chromatography (9:1, petroleum ether:ether) affords an oil in 79% yield. Rf = 0.33 (4:1, petroleum ether: ether). Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.03; H, 9.17. ^{1}H Nmr ($CDCl_3$): δ 0.85 (t, J = 7, 3H), 1.1-1.9 (m, 12H), 2.05 (m, 1H), 3.05 (dt, J= 4.4 and 6, 1H), 3.9 (s, 4H), 4.4 (AB_q, J = 12, 1H), 4.6 (AB_q, J = 12, 1H), 7.2-7.3 (m, 5H). ^{13}C Nmr ($CDCl_3$): δ 14.0, 22.9, 27.5, 28.4, 31.4, 32.5, 38.2, 39.9, 64.1, 70.5, 80.2, 108.3, 127.2, 127.5, 128.1, 138.9.

***trans*-2-n-Butyl-3-benzyloxycyclohexanone (7).** Ketal (6) (2.4 g; 7.9 mmol) was dissolved in 20 ml THF followed by the addition of 5 ml of 20% HCl. The mixture was warmed to 60 ^{0}C for 2 h while monitoring the reaction by gc for disappearance of 6. The reaction mixture was cooled to

room temperature and diluted with 100 ml of ethyl acetate followed by slow addition of 50 ml of saturated sodium carbonate. The aqueous layer was extracted twice more with 50 ml portions of ethyl acetate, the organic layers were combined and washed with brine, dried over magnesium sulfate, filtered and concentrated. Generally, an oil is obtained in quantitative yield and in sufficient purity to proceed to the next step. If necessary, flash chromatography may be conducted. Rf = 0.30 (5:1, petroleum ether:ether). Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.22; H, 9.43. ^{1}H Nmr ($CDCl_3$): δ 0.75 (t, J = 7, 3H), 1.0-1.3 (m, 6H), 1.8-2.1 (m, 5H), 2.4-2.45 (m, 1H), 2.6 (dd, J = 13 and 4, 1H), 3.4 (dd, J = 9 and 5, 1H), 4.45 and 4.5 (AB_q, J = 17, 2H), 7.15-7.25 (m, 5H). ^{13}C Nmr ($CDCl_3$): δ 13.8, 22.5, 27.2, 28.7, 31.9, 37.2, 41.4, 42.5, 70.5, 76.7, 127.3, 127.4, 128.2, 138.4, 211.0.

***trans*-N-Benzyl-5-benzenesulfonyl-7-n-butyl-8-benzyloxy-1-azaspiro[5.5]undecan-2-one (9).** Benzylamine (0.535 g; 5 mmol) was added to a solution of ketone (**7**) (1.3 g; 5 mmol) in 5 ml of dry benzene. The reaction mixture was stirred for 0.5 h and the solvent was removed by rotary evaporation at 40 ^{0}C. The process was repeated until azeotropic removal of water showed predominantly imine (**8**) formation by nmr (δ 4.6, Ph-C$\underline{H}_2$-N). The imine (**8**) was dissolved in 5 ml of THF and chilled to -78 ^{0}C and boron trifluoride etherate (0.71 g; 5 mmol) was added resulting in a cloudy suspension. In a separate flask, 4-phenylsulfonylbutanoic acid (1.37 g; 6 mmol) was dissolved in 65 ml of THF and chilled to -78 ^{0}C. n-Butyllithium (5.1 ml; 12 mmol; 2.35 M in hexane) was added giving a yellow-gold solution. The mixture was stirred for 0.5 h and the activated imine solution was added *via* positive pressure cannula to the dianion solution. Much of the cloudiness and color dissipated immediately and upon clearing the dry-ice bath was removed and replaced by a 0 ^{0}C bath for 1.0 h. Trifluoroacetic anhydride (1.9 g; 9.2 mmol) was added, the cold bath was removed and stirring was continued for another 0.5 h. The reaction mixture was poured into a separatory funnel containing 75 ml of 50% sodium carbonate and 75 ml of ether. The aqueous layer was extracted twice with 50 ml portions of ether, the organic layers were combined and washed with 100 ml of brine. Drying over sodium sulfate, filtration, and

concentration yielded a off-yellow oil that converted to an amorphous foam under high vacuum (0.1 mm Hg) (2.5 g, 89% of diastereomers). Flash chromatography (100% ether) affords non-polar (**9a** 1.29 g; 46%) and polar (**9b**; 1.08 g; 39%) compounds. Recrystallization was accomplished with chloroform-ether-petroleum ether mixtures. Anal. Calcd for $C_{34}H_{41}NO_4S$: C, 72.95; H, 7.38; N, 2.50. Found: C, 72.78; H, 7.24; N, 2.47.

Non-polar diastereomer (9a): mp = 117-118 °C. Rf = 0.15 (100% ether). ^{1}H Nmr ($CDCl_3$): δ 0.85 (t, J = 7, 3H), 1.05-1.25 (m, 5H), 1.5-1.9 (m, 5H), 2.0-2.4 (m, 4H), 2.55 (m, 2H), 2.9 (m, 1H), 3.2 (dt, J = 6.3 and 3.4, 1H), 3.6 (t, J = 5, 1H), 4.4 (AB_q, J = 12, 2H), 4.9 (s, 2H), 7.15-7.4 (m, 10H), 7.55-7.7 (m, 3H), 7.85 (dd, J = 7, 2H). ^{13}C Nmr ($CDCl_3$): δ 14.0, 18.9, 22.8, 24.6, 27.8, 29.2, 29.8, 32.5, 38.8, 38.9, 39.2, 46.7, 62.3, 65.6, 69.8, 126.6, 126.9, 127.4, 127.5, 128.0, 128.3, 129.5, 133.9, 138.6, 139.0, 139.9, 170.7.

Polar diastereomer (9b): mp = 114-117 °C. Rf = 0.10 (100% ether). ^{1}H Nmr ($CDCl_3$): δ 0.9 (t, J = 7, 3H), 1.1-1.4 (m, 4H), 1.55-1.9 (m, 5H), 2.1-2.2 (m, 3H), 2.6-2.7 (dq, J = 5 and 9, 1H), 2.75 (q, J = 9, 1H), 2.9 (m, J = 9, 1H), 3.1 (m, 1H), 3.35 (t, J = 5, 1H), 4.35 (AB_q, J = 12, 2H), 4.9 (AB_q, J = 17, 2H), 7.2-7.4 (m, 10H), 7.6-7.75 (m, 3H), 7.9 (d, J = 8, 2H). ^{13}C Nmr ($CDCl_3$): δ 13.9, 18.0, 23.0, 25.8, 27.0, 28.7, 32.7, 35.6, 37.1, 38.3, 47.8, 61.9, 67.9, 69.5, 78.6, 126.6, 127.0, 127.3, 127.4, 128.1, 128.2, 129.4, 133.9, 138.1, 138.7, 139.5, 173.2.

***trans*-N-Benzyl-7-n-butyl-8-benzyloxy-1-azaspiro[5.5]undecan-2-one (10).** The benzenesulfonyl-azaspiran (0.25 g; 0.45 mmol; **9a** or **9b**) was dissolved in 10 ml anhydrous methanol and chilled to 0 °C with stirring. Na-Hg amalgam (6%) was added in 0.050 g portions in 15 min intervals until all the starting material was consumed. The reaction mixture was diluted with 20 ml of anhydrous ether and filtered through a frit of Celite. The solution was evaporated to an oil and chromatographed (1:1, petroleum ether:ether) to afford the spirolactam (**10a**) as an oil (0.06 g; 33%) and the E/Z mixture of elimination products (**10b**) (0.078 g; 43%). Note: Sodium hydrogen

phosphate had little effect.[11]

Spirolactam (10a): Ms (m/z, M^+) calcd 419.2824: found 419.2821. ^{1}H Nmr ($CDCl_3$): δ 0.85 (t, J = 7, 3H), 1.1-1.4 (m, 8H), 1.6-1.9 (m, 7H), 2.1-2.2 (m, 2H), 2.5 (t, J = 5, 2H), 3.3 (bs, 1H), 4.45 (dq, J = 12 and 3, 2H), 4.7 and 4.75 (AB_q, J = 16, 2H), 7.1-7.4 (m, 10H). ^{13}C Nmr ($CDCl_3$): δ 14.0, 16.7, 22.8, 23.3, 29.7, 30.5, 32.2, 33.1, 35.0, 35.4, 38.4, 45.6, 59.9, 69.9, 76.3, 126.1, 127.4, 127.45, 128.1, 128.3, 138.9, 139.7, 171.4.

Elimination product (10b): Ms (m/z, M^+) calcd 419.2824: found 419.2821. ^{1}H NMR ($CDCl_3$): δ 0.9 (t, J = 7, 3H), 1.1-1.4 (m, 6H), 1.5-2.1 (m, 5H), 2.2 (t, J = 7, 2H), 2.3-2.4 (m, 3H), 2.5 (dt, J = 14 and 5, 1H), 3.2 (dt, J = 8 and 3, 1H), 4.4 (d, J = 6, 2H), 4.55 and 4.6 (AB_q, J =12, 2H), 5.1 (t, J = 7, 1H), 5.9 (bs, 1H), 7.2-7.4 (m, 10H). ^{13}C Nmr ($CDCl_3$): δ 14.1, 23.0, 23.7, 25.1, 28.9, 30.0, 31.5, 37.0, 38.8, 43.0, 43.5, 70.5, 80.5, 120.5, 127.2, 127.3, 127.4, 127.6, 128.1, 128.5, 138.3, 138.5, 139.0, 172.2.

***trans*-N-Benzyl-5-benzenesulfonyl-7-n-butyl-8-benzyloxy-1-azaspiro[5.5]undecane (11).** The azaspiran (**9a** or **9b;** 0.15 g; 0.27 mmol) was dissolved in 5 ml of THF and chilled to 0 °C. Borane•THF complex (0.3 ml; 1 M solution) was added and the cold bath was removed. After stirring for 0.25 h an additional 0.2 ml of borane•THF complex was added and the reaction mixture monitored for loss of **9** by tlc. Upon completion, 20 ml of 0.01 M NaOH was added and the mixture was extracted (3 x 50 ml of ethyl acetate). The organic layers were combined and dried over sodium sulfate, filtered and concentrated *in vacuo* to afford a foam. Flash chromatography (ether) yields 0.131 g (90%) of the amine as a semi-solid. Note: Rapid addition of borane will give a large amount of elimination product similar to **10b**. Ms (m/z, M^+) calcd 545.2953: found 545.2952 (dev -2.2 ppm). ^{1}H Nmr ($CDCl_3$): δ 0.8 (t, J = 7, 3H), 1.0-1.3 (m, 6H), 1.5-1.7 (m, 2H), 1.75-2.3 (m, 8H), 2.4 (dd, J = 4 and 14, 1H), 2.55 (d, J = 14, 1H), 2.8 (t, J = 12, 1H), 3.2 (dt, J = 4.4 and 10, 1H), 3.25 (dd, J = 3.5 and 13, 1H), 3.55 (AB_q, J = 13, 1H), 4.0 (AB_q, J = 13, 1H), 4.5 (AB_q, J =

12, 1H), 4.65 (AB_q, J = 12, 1H), 7.2-7.4 (m, 10H), 7.5-7.65 (m, 3H), 7.9 (d, J = 9, 2H). ^{13}C Nmr ($CDCl_3$): δ 14.1, 18.0, 23.1, 23.2, 25.3, 27.7, 28.6, 31.5, 37.1, 38.6, 39.3, 47.4, 60.3, 64.3, 70.8, 81.8, 126.8, 127.4, 127.9, 128.2, 128.3, 128.4, 129.0, 133.3, 139.2, 139.7, 139.8.

N-Benzyl-5-benzenesulfonyl-1-azaspiro[5.5]undecan-2-one (12).[3a] Isolated as an oil. ^1H Nmr ($CDCl_3$): δ 1.0-1.2 (m, 3H), 1.45-1.95 (m, 7H), 2.0-2.2 (m, 1H), 2.5 (dd, J = 18 and 9, 1H), 2.8-2.9 (m, 1H), 3.8 (d, J = 4, 1H), 4.8 (s, 2H), 7.1 (t, J = 7, 1H), 7.25, (t, J = 8, 2H), 7.35, (t, J = 8, 2H), 7.5-7.65 (m, 3H), 7.9 (d, J = 7.5, 2H). ^{13}C Nmr ($CDCl_3$): δ 18.0, 22.9, 23.0, 25.0, 27.3, 33.5, 39.1, 45.0, 59.6, 62.5, 126.6, 127.4, 128.0, 128.3, 129.5, 133.9, 139.5, 139.8, 170.2.

Elimination Product (13). Isolated as an oil. Procedure identical to the preparation of **10a/10b.** ^1H Nmr ($CDCl_3$): δ 1.5 (m, 6H), 2.1 (t, J = 5, 2H), 2.15 (t, J = 5.5, 2H), 2.3 (dt, J = 7 and 2, 2H), 2.4 (q, J = 7, 2H), 4.5 (d, J = 6, 2H), 5.1 (t, J = 7, 1H), 5.8 (bs, 1H), 7.3-7.4 (m, 5H).

ACKNOWLEDGMENTS

The author wishes to thank Loyola University of Chicago for the purchase of the Varian VXR-300 MHz nmr used in this study and kind financial support through the BRSG. This work also was supported, in part, by the National Institutes of Health (ES04434). Dr. Doris Hong (Northwestern University) is gratefully acknowledged for conducting the mass spectral analyses.

REFERENCES

1. Some recent examples include: a) G. Stork and K. Zhao, J. Am. Chem. Soc., 1990, **112**, 5875. b) J. Zhu, J. C. Quirion, and H. P. Husson, Tetrahedron Lett., 1989, **30**, 6323. c) P. Duhamel, M. Kotera, T. Montiel, B. Marabout, and D. Davoust, J. Org. Chem., 1989, **54**, 4419. d) J. Venit, M. DiPierro, and P. Magnus, J. Org. Chem., 1989, **54**, 4298. e) D. Tanner,

M. Sellen, and J. E. Backvall, J. Org. Chem., 1989, **54**, 3374. f) S. P. Tanis and L. A. Dixon, Tetrahedron Lett., 1987, **28**, 2495. g) J. D. Winkler, P. M. Hershberger, and J. P. Springer, Tetrahedron Lett., 1986, **27**, 5177. h) D. Tanner and P. Somfai, Tetrahedron, 1986, **42**, 5657. i) C-K. Sha, S-L. Ouyang, D-Y. Hsieh, R-C. Chang, and S-C. Chang, J. Org. Chem., 1986, **51**, 1490. j) P. Duhamel, M. Kotera, and T. Monteil, Bull. Chem. Soc. Japan, 1986, **59**, 2353. k) W. Gessner, K. Takahashi, B. Witkop, A. Brossi, and E. X. Albuquerque, Helv. Chim. Acta, 1985, **68**, 49. l) S.C. Carey, M. Aratani, M., and Y. Kishi, Y., Tetrahedron Lett., 1985, **26**, 5887. m) T. Ibuka, H. Minakata, M. Hashimoto, L. E. Overman, and R. L. Freerks, Heterocycles, 1984, **22**, 485. n) S. A. Godleski, D. J. Heacock, J. D. Meinhart, and S. Van Wallendael, J. Org. Chem., 1983, **48**, 2101. o) W. Carruthers and S. A. Cumming, J. Chem. Soc. Perkin Trans. I., 1983, 2383. p) A. J. Pearson and P. Ham, J. Chem. Soc. Perkin Trans. I., 1983, 1421. q) G. E. Keck and J. B. Yates, J. Org. Chem., 1982, **47**, 3591. r) For studies prior to 1982 see: Y. Inubushi and T. Ibuka, Heterocycles, 1982, **17**, 507.

2. a) T. Ogura and A. Warashina, Comp. Biochem. Physiol. C., 1987, **88C**, 249. b) B. Witkop and E. Gossinger, "Amphibian Alkaloids" in The Alkaloids, Vol. 21 Ed., Brossi, A., Academic Press, New York, **1983**, p. 168. c) K. Takahashi, B. Witkop, A. Brossi, M. A. Maleque, and E. X. Albuquerque, Helv. Chim. Acta, 1982, **65**, 252.

3. a) C. M. Thompson, D. L. C. Green, and R. Kubas, J. Org. Chem., 1988, **53**, 5389. For the synthesis and further application of 4-PSBA see: b) C. M. Thompson and J. A. Frick, J. Org. Chem., 1989, **54**, 890.

4. P. A. Wender, J. M. Erhardt, and L. J. Letende, J. Am. Chem. Soc., 1981, **103**, 2114.

5. E. J. Corey, L. S. Melvin, and M. F. Haslanger, Tetrahedron Lett., 1975, 3117.

6. M. J. Eis, J. E. Wrobel, and B. Ganem, J. Am. Chem. Soc., 1984, **106**, 3693.

7. Chelation control in asymmetric synthesis has been reviewed. See for example: M. T. Reetz Angew. Chem. Int. Ed. Engl. 1984, **23**, 556.

8. Preliminary results also indicate that vinyllithium and methyllithium led to regiochemical mixtures of hydroxy ketals. Grignard reagents were somewhat ineffective.

9. Al-Hg see: a) M. C. Mussatto, D. Savoia, C. Trombini, and A. Umani-Ronchi, J. Org. Chem., 1980, **45**, 4002. Bu_3Sn-H see: b) A. B. Smith, K. J. Hale, and J. P. McCauley, Tetrahedron Lett., 1989, **30**, 5579. Zn-HOAc see: c) H. O. House and J. L. Larson, J. Org. Chem., 1968, **33**, 61.

10. W. C. Still, M. Kahn, and A. Mitra, J. Org. Chem., 1975, **43**, 2923.

11. B. M. Trost, H. C. Arndt, P. E. Strege, and T. R. Verhoeven, Tetrahedron Lett., 1976, 3477.

Received, 6th January, 1992