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Chemistry of the Hexahydropyrrolo[2,3-*b*]indoles: Configuration, Conformation, Reactivity, and Applications in Synthesis

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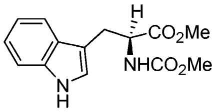
ABSTRACT
The stereoselective formation of 2-endo-substituted hexahydropyrrolo[2,3-*b*]indoles from 2-substituted tryptamine derivatives, especially tryptophan, is discussed. Parallels are drawn with the formation of related heterocyclic systems, such as the hexahydrofurano[2,3-*b*]benzofurans, in which the thermodynamic preference of a substituent at the 2-position is also for the endo-configuration. Functionalization of tryptophan-derived hexahydropyrroloindoles at positions 2-, 3-, and 3a- is discussed with special emphasis on the 2-position, at which both radical and nucleophilic reactions take place preferentially on the endo-face of the diazabicyclo[3.3.0]-octane system. The kinetic and thermodynamic preference for the 2-endo-position is considered in terms of the minimization of torsional strain, and parallels are drawn to the Woerpel model for the reactivity of analogous five-membered cyclic oxacarbenium ions. The use of the tryptophan-derived hexahydro[2,3-*b*]pyrroloindoles in the stereocontrolled synthesis of amino acids and alkaloids is presented.

Introduction

The hexahydropyrrolo[2,3-*b*]indole skeleton is a key structural element in a wide selection of alkaloids exhibiting a diverse range of biological activities.[1,2] As such, the chemistry of this class of heterocycles has been of interest since the early studies of Julian and Pikl[3], and of King and Robinson,[4] on the synthesis of the calabar bean alkaloid physostigmine.[5,6] More recently, interest in several hexahydropyrroloindole-based alkaloids (Chart 1), including the quadrigemines,[7] himastatin,[8] amauromine,[9] tryprostatin,[10] brevianamides,[10,11] gypsetin,[10] and roquefortine C,[12] as well as the role of this nucleus as a key intermediate structure en route to related alkaloids such as the okaramines[13] and the structurally novel CJ-12662,[14] has led to a resurgence of interest in this domain. Work in our laboratory in this area began several years ago with the application of the hexahydropyrrolo[2,3-*b*]indole tautomers of tryptophan as key intermediates in the asymmetric synthesis of α-alkyltryptophan derivatives from tryptophan itself. This initial foray expanded into a wide ranging study of the factors affecting the formation and reactivity of the hexahydropyrroloindoles, which we summarize in this Account.



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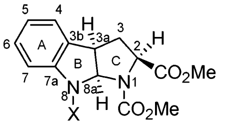

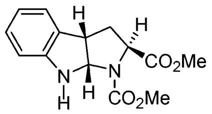

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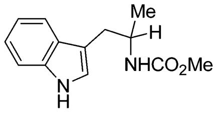
2: X = H
4: X = Ac
5: X = SO_2Ph
6: X = SO_2-4-CH_3Ph
7: X = SO_2-4-OMePh
8: X = SO_2Me

Configuration and Conformation of the Hexahydropyrroloindoles and Related Heterocycles: Kinetic and Thermodynamic Cyclization of Tryptophan Derivatives. It was established early by Hino and co-workers that *N*-methoxycarbonyl L-tryptophan methyl ester **1** tautomerizes in strong acid media to give a mixture of the hexahydropyrroloindoles **2** and **3** in which the CO_2Me endo-isomer **2** predominates.[1,15] In 85% phosphoric acid, the optimum reagent for ring closure, the thermodynamic ratio is approximately 9:1 in favor of **2**. In aqueous acid, **1** is rapidly regenerated from **2** and **3**, but the hexahydropyrroloindole form can be stabilized by acylation on N-8 (**4**) as demonstrated by Hino. In our laboratory, we have preferred sulfonylation on the initial mixture of **2** and **3** as this typically provides the N-8 sulfonyl derivatives as highly crystalline single diastereomers **5**−**8**.[16−19] Under the sulfonylation conditions, the less stable minor exo-isomer typically reverts to **1** which, combined with the crystallinity of **5**−**8**, greatly facilitates the production of these substances on a significant scale without recourse to chromatographic purification.



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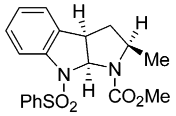

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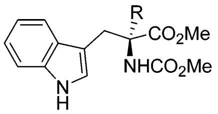
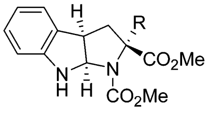
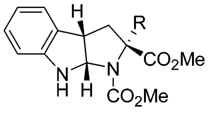


11: R= Me
12: R= Et
13: R= ${}^{i}Pr$



14: R = Me
15: R = Et
16: R = ${}^{i}Pr$



17: R = Me
18: R = Et
19: R = ${}^{i}Pr$

X-ray crystallographic studies of numerous members of this series of compounds, as exemplified by **5** (Figure

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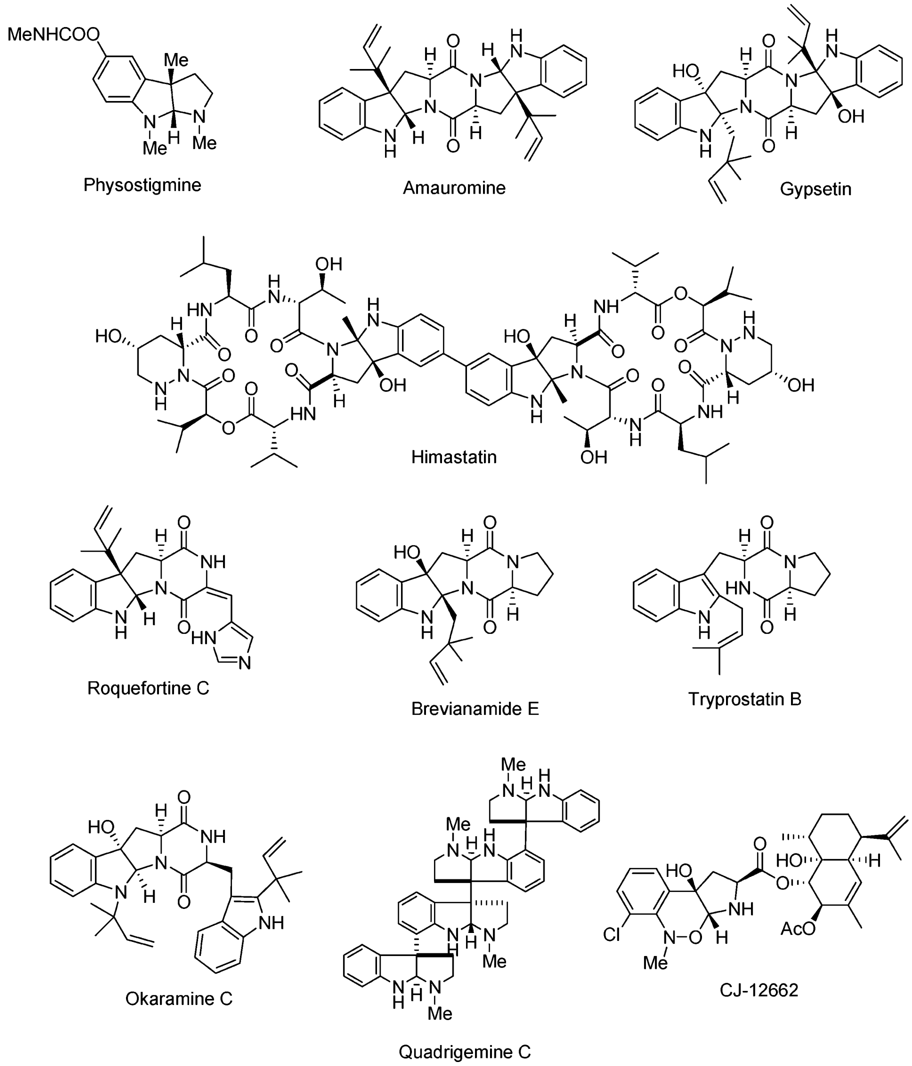
10.1021/ar050175j CCC: $37.00

Chart 1



1),[20] revealed a common feature: the adoption of an envelope-like conformation by the C-ring with the flap (C-2) puckered in toward the endo-surface of the ring system, placing the ester group directly under the A ring. This conformation, which is not an artifact of crystal packing, also predominates in solution as revealed by the typical upfield shift of the ester methyl group ($\delta \sim 3.10$), because of shielding by the aromatic ring current, and by the absence of ^3J coupling of H-3endo to both H-2 and H-3a. Indeed, these two features of the ^{1}H-NMR spectrum are highly diagnostic of endo-substitution at C-2. The C-2 exo-substituted isomers exhibit more typical chemical shifts for the ester methyl group and have an alternative conformation of the C-ring, as established both spectroscopically and crystallographically.

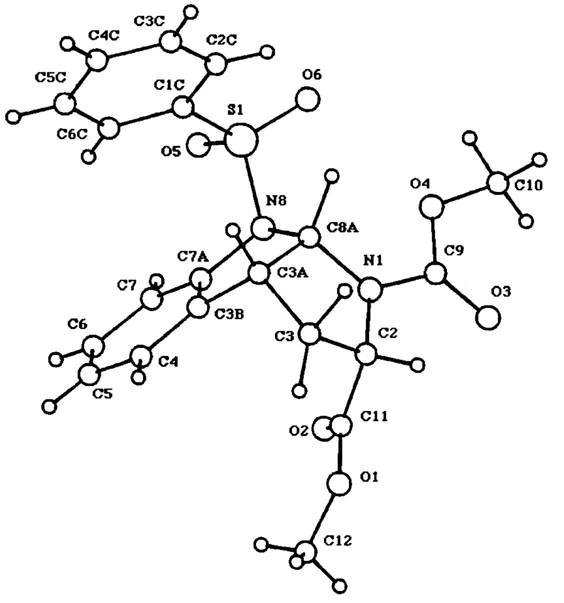
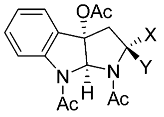


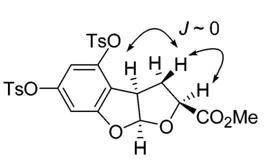
FIGURE 1. X-ray crystal structure of **5**.

The thermodynamic preference for the C-2 endo-substituted isomers is not limited to carbomethoxy substituents as it was readily demonstrated that the α-methyl tryptamine derivative **9** also afforded the endo-substituted pyrroloindole **10** preferentially under the same equilibrating reaction conditions with subsequent sulfonylation.[21] When the α-alkylated tryptophan derivatives **11**−**13** were subject to ring closure with trifluoroacetic acid in $CDCl_3$ the alkyl endo-products **14**−**16** predominated over the alkyl exo-isomers **17**−**19**. Moreover, the preference for the alkyl endo-isomer was greater in the isopropyl and ethyl series (~3.8:1) than in the methyl series (~1.4:1). Thus, although tempting at first sight (Figure 1), attractive $\pi-\pi$ interactions between the arene and the ester carbonyl system are not the main driving force behind the preferential formation of **2** (**5**) rather than **3**.[21]



20: X = CO_2Me, Y = H
21: X = H, Y = CO_2Me

It is also evident that the preference of C2 substituents for the endo- over the exo-position holds under basic as well as acidic conditions as **20** undergoes inversion at C2 on treatment with potassium *tert*-butoxide in dimethyl formamide to give **21**.[22]



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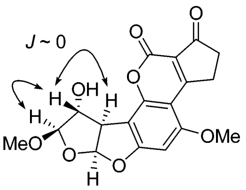

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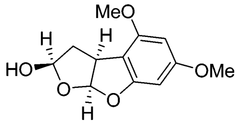

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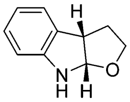

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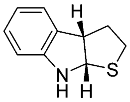

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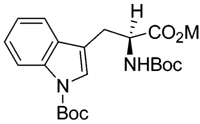
In the crystal (Figure 1) and solution conformation of **5** and its many C-2 endo-substituted relatives, the C-2 substituent is close to orthogonal to the plane of the partial N1-CO_2Me double bond, as is the case in the preferred conformation of *N*-Boc proline derivatives,[23] thereby minimizing ^{1,3}A strain.[24] However, while the minimization of allylic strain certainly contributes to the preferential formation of **2** and its congeners over **3**, it is by no means the only factor. Indeed, physostigmine with the sp^3 hydridized N1 and the absence of C2 subsitutents is also revealed to prefer a conformation in which C2 is puckered toward the endo-surface by X-ray crystallography.[25] It is therefore apparent that the minimization of torsional strain around the five-membered C-ring plays a significant role in the configurational and conformational equilibria of **1** with **2** and **3**, which is amply supported by molecular mechanics type calculations.[21]

Furthermore, the hexahydrofuro[2,3-*b*]benzofuran skeleton, common to the aflatoxins, shows a significant preference for C2 substituents to adopt the endo-configuration under equilibrating conditions as demonstrated by the experimental work of Civitello and Rapoport,[26] Harris and co-workers,[27] and Townsend and co-workers[28] with systems **22**, **23**, and **24**, respectively, and by computational work by Messeguer and co-workers[29] and Morales-Rios et al.[30] The Morales-Rios group also has carried out spectroscopic and computational studies on the hexahydrofuro[2,3-*b*]indole **25** and the hexahydrothieno[2,3-*b*]indole **26** skeletons and find that, in common with the pyrrolo[2,3-*b*]indole and furo[2,3-*b*]-benzofurans, the predominant conformation has C2-puckered in toward the endo-surface.[31] Overall, the preference for C2 substituents for the endo-configuration and for the C2 carbon to adopt an endo-conformation in this entire series of bicyclo[3.3.0]octane-based heterocycles appears to be primarily driven by the relief of torsional strain. Under equilibrating conditions, 2-alkylbicyclo[3.3.0]-octan-1-ones are 1:1 mixtures of exo- and endo-isomers, suggesting that similar factors exist in related carbocyclic systems, albeit to a lower extent.[32,33] This fundamental preference for the endo-configuration and conformation may be further enhanced by factors such as the minimization of allylic strain when the C1 center is sp^2 hybridized and, possibly, by $\pi-\pi$ attractive interactions with appropriate substituents (Figure 1).



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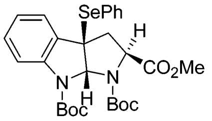

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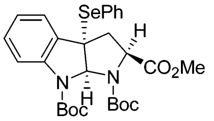
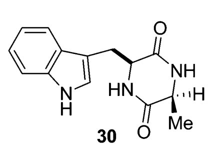


29

When the kinetic C2 exo-isomers of the 2-substituted hexahydropyrrolo[2,3-*b*]indoles are required, it is necessary to retard the equilibration step. As first demonstrated by Danishefsky and co-workers,[9] and as studied extensively in our laboratory,[34] this may be achieved with selenium-based electrophiles. Thus, treatment of **27**, and related derivatives, with *N*-phenylselenophthalimide and *p*-toluenesulfonic acid in dichloromethane results in the formation of a 9:1 ratio of the exo- and endo-products **28**, and **29**. The base-catalyzed epimerization of **28** to *ent*-**29** establishes the kinetic nature of this product.[34]



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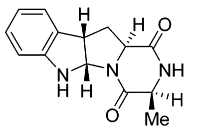

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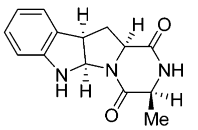

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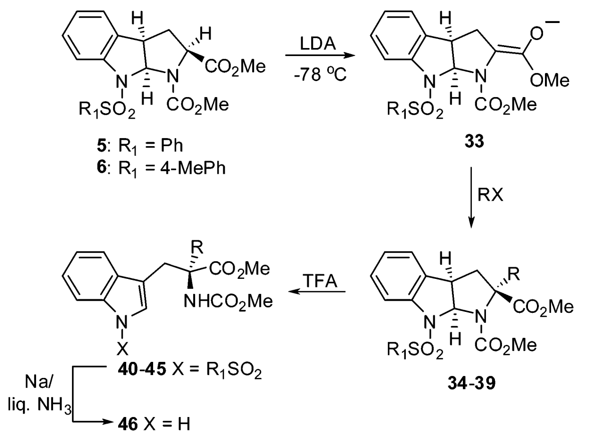
Finally, as recognized by Hino and co-workers,[35] the acid-catalyzed cyclization of tryptophan-based diketopiperazines **30** gives the exo-isomers **31**.[36] Presumably, this is due to the high degree of strain that would be engendered in the N1-CO partial double bond in the endo-isomer **32**.

Scheme 1. Alkylation with Retention of Configuration



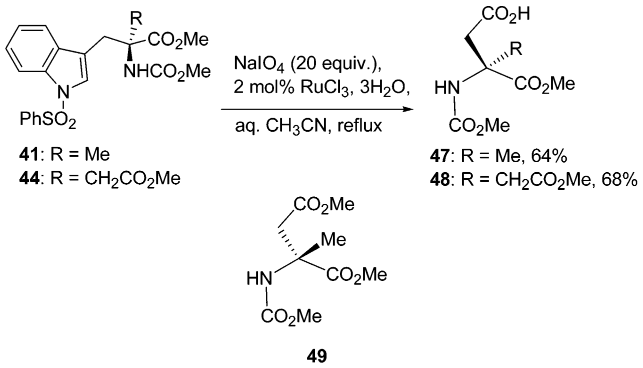
Enolate Reactions: Asymmetric Synthesis of 2-Alkyl Tryptophan Derivatives.[16,17] Deprotonation of sulfonamides **5** or **6** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C leads to the formation of an enolate anion **33**, which is alkylated with a variety of alkyl halides, selected to mimic the side chains of other amino acids, in high yield. The alkylation took place with complete selectivity on the exo-face as evident from the ^{1}H-NMR chemical shift of the methyl ester in the various products (Table 1). Although the early work was conducted with the *p*-toluenesufonamide **6**, the benzenesulfonamide **5** was preferred subsequently owing to its higher crystallinity. Interestingly, when the same conditions were applied to the methanesulfonamide **8**, deprotonation and alkylation took place at the mesyl methyl group rather than at C2. Subsequent treatment of the C2 alkyl derivatives with trifluoroacetic acid (TFA) in dichloromethane followed by exposure to sodium in liquid ammonia regenerated the tryptophan skeleton (Scheme 1, Table 1). Overall, the process of formation of **5** or **6** followed by alkylation and ring cleavage constitutes a novel example of Seebach's principle of self-regeneration of chirality[37] and enables the formation of a range of α-alkyl L-tryptophan derivatives from L-tryptophan itself with complete retention of configuration.[38,39]

Table 1. Alkylation with Retention of Configuration

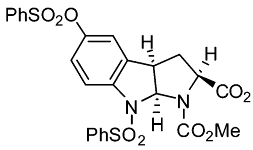
R	R_1 (amino acid side chain)	alkylation product (% yield)	ring-opening product (% yield)
4-MePh	$CH_2CH{=}CH_2$ (−)	**34** (79)	**40** (85)
Ph	CH_3 (alanine)	**35** (95)	**41** (100)
4-MePh	$PhCH_2$ (phenylalanine)	**36** (71)	**42** (93)
4-MePh	$(CH_2)_2SMe$ (methionine)	**37** (33)	**43** (84)
Ph	CH_2CO_2Me (methyl aspartate)	**38** (100)	**44** (100)
4-MePh	$CH_2O(CH_2)_2SiMe_3$ (serine)	**39** (78)	**45** (61)

Oxidative cleavage of the indole ring in **41** with catalytic ruthenium trichloride and sodium metaperiodate gave the α-methyl-L-aspartate **47** (Scheme 2). Alternatively, oxidative cleavage of **44** gave the enantiomerically pure α-disubstituted amino acid derivative **48**, whose chirality derives solely from the differential protection of the two side chains. Barton decarboxylation of this substance then gave the α-methyl-D-aspartate **49** (Scheme 2). In this manner, efficient asymmetric syntheses of both enantiomers of α-methyl aspartic acid were achieved from a single chiral building block **5**.[18]

Scheme 2. α-Methyl Aspartate Synthesis



Starting from L-5-hydroxytryptophan, the hexahydropyrroloindole **50** was prepared in the standard manner. Deprotonation and alkylation of this substance afforded the alkylated derivatives **51**−**54**, in good yield with complete retention of configuration, and these could be converted to the corresponding 5-hydroxytryptophan derivatives **55**−**57** with trifluoroacetic acid. Birch reduction of **55** and saponification afforded a simple synthesis of enantiomerically pure L-α-methyl-5-hydroxytryptophan **58**.[19]



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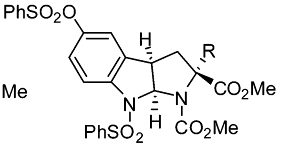
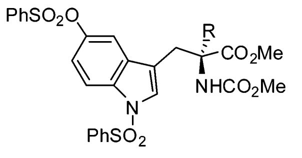
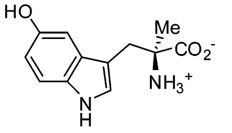


51: R = Me
52: R = Bn
53: R = $CH_2CH{=}CH_2$
54: R = $CH_2O(CH_2)_2SiMe_3$



55: R = Me
56: R = Bn
57: R = $CH_2CH{=}CH_2$



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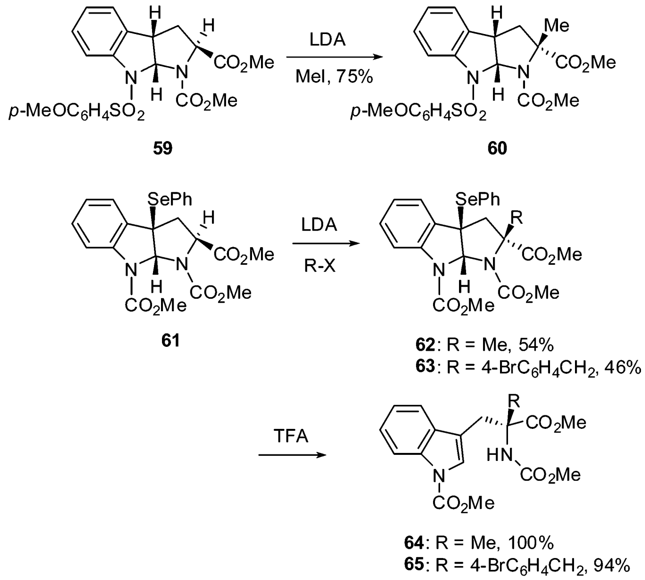
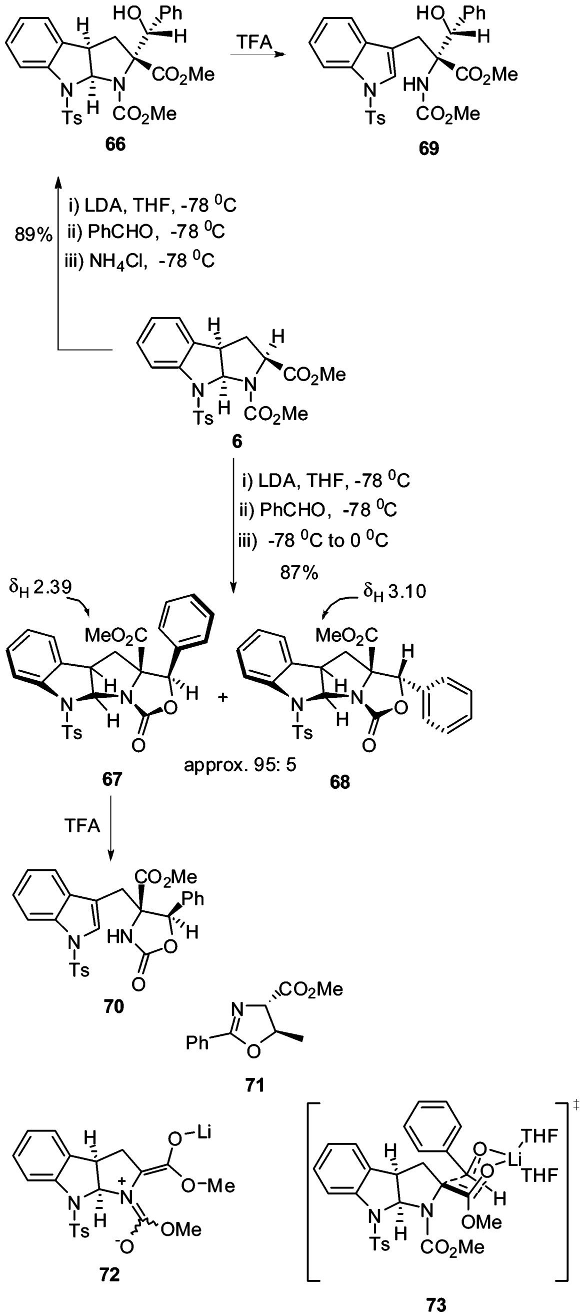
Self-evidently, the α-alkylated D-tryptophans can be obtained by the operation of the above chemistry starting from D-tryptophan. However, the alternative possibility of the alkylation of the kinetic exo-carboxylates, corresponding to **3**, with inversion of configuration is more appealing when the cost of D-tryptophan is taken into account. The feasibility of this alkylation with clean inversion was demonstrated by the conversion of **59** to **60** in 75% yield on treatment with LDA and then methyl iodide,[20] but this process was not practical owing to the very low yields of **3** and its N-sulfonylated derivatives under the conditions of the equilibrating ring closure reaction. With the development of the kinetic, *N*-phenylselenophthalimide mediated ring closure, and the preparation of the exo-carbomethoxy pyrroloindole **61** in high yield, this approach was

Scheme 3. Alkylation with Inversion of Configuration



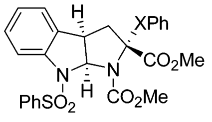
Scheme 4. Diastereoselective Aldol Condensation



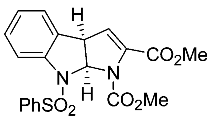
greatly facilitated. Thus, treatment of **61** with LDA and the appropriate alkyl halide in the usual manner afforded **62** and **63** in good yield with clean inversion of configuration (Scheme 3).[34] The presence of the bulky phenylseleno group on the exo-surface of the enolate does not interfere with the exo-selective alkylation process. Cycloreversion and cleavage of the phenylseleno group was affected in the usual manner with trifluoroacetic acid giving the two D-tryptophan derivatives **64** and **65**.

When the lithium enolate of **6** was treated with benzaldehyde at −78 °C and the reaction was quenched at the same temperature, a single diastereomeric aldol **66** was formed in excellent yield (Scheme 4). When the reaction mixture was allowed to come to room temperature before quenching, cyclization onto the carbamate took place to give the tetracyclic products **67** and **68** in excellent yield and with very high diastereocontrol (Scheme 4).[40] The stereochemical attribution of **67**, and, by implication, that of **66**, follows from the highly unusual upfield shift of the methyl ester sandwiched[41] between the two aromatic rings. As in the alkylations, treatment of both **66** and **67** with trifluoroacetic acid resulted in cycloreversion to the tryptophan skeleton (Scheme 4). Analogous results were observed with hexanal and with cyclohexanone as electrophile in these aldol condensations. While the high degree of exo-selectivity in these reactions was expected in view of the earlier alkylations, the excellent stereocontrol at the second asymmetric center was less so. Indeed, Seebach et al., in their studies on the self-reproduction of chirality, observed very poor control at the aldol center when aldehydes were condensed with exocyclic enolates, such as the one derived from the threonine derivative **71**.[42] We rationalize the observed high selectivity in terms of the formation of a single enolate **72** from **6** on treatment with LDA, which is preferred because of the minimization of dipolar interactions between the enolate and the N-1 carbamate. This enolate then undergoes reaction with the aldehyde through a single Zimmerman−Traxler-like transition state **73**.

Functionalization at C3.[43,44] Treatment of **5** with LDA followed by quenching with either phenylselenyl chloride or diphenyl disulfide gave the chalcogenides **74** and **75**, both with complete exo-selectivity, in excellent yield. Subsequent oxidation with magnesium monoperoxyphthalate in THF, or methanol at room temperature, resulted in the formation of the tetrahydropyrroloindole **76** in excellent yield. The unusually low temperature at which the sulfoxide elimination occurred suggested that a syn-elimination is not involved and that the sulfoxide or selenoxide is expelled by the lone pair on the carbamate nitrogen to give the acyl iminium ion **77**, from which **76** is formed by deprotonation. This hypothesis was supported by the isolation of the byproduct **78**, arising from exo-face attack on **77** by the solvent, when these reactions were run in methanol.[45]



74: X = Se
75: X = S



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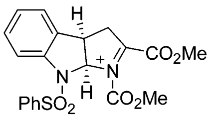
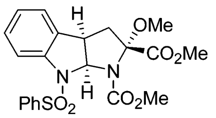
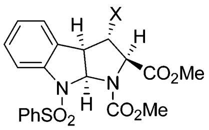


77

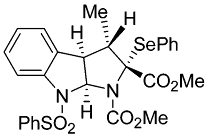


78

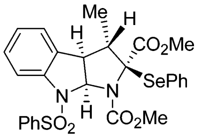
Conjugate addition reactions to **76** with Lipshutz and Sengupta higher order cuprates[46] took place with excellent diastereoselectivity on the exo-surface and were followed by equally exo-selective quenchings of the intermediate enolate anion. Equally selective conjugate addition reactions were also observed with heteroatom nucleophiles. Deprotonation of **79** with LDA followed by quenching with phenylselenyl chloride gave the adduct **83** as a 2:1 exo: endo mixture of isomers, thereby demonstrating for the first time the possibility of reactions on the endo-surface of the hexahydropyrroloindole when circumstances conspire against attack on the more exposed exo-surface. Treatment of endo-**83** with magnesium monoperoxyphthalate resulted in the formation of **84** which, on exposure to Pearlman's catalyst and hydrogen in methanol, afforded **85**.



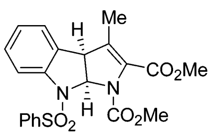
79: X = Me, 79%
80: X = ^{n}Bu, 60%
81: X = ^{t}Bu, 70%
82: X = Ph, 65%



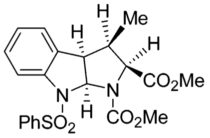
83 *exo*



83 *endo*

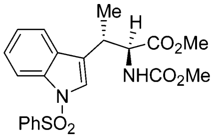


84

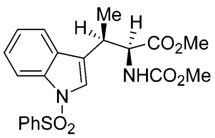


85

Ring opening of **79** and **85** was achieved with trifluoroacetic acid in the usual way, albeit with significant differences in rate, to give **86** and **87**. Thus, while **85** with its 3-endo-methyl group opened in an hour at room temperature, the 3-exo-methyl isomer **79** required between 3 and 4 days under the same conditions. Interestingly, the 3-exo-*tert*-butyl derivative **81** was unchanged after several months on standing in neat trifluoroacetic acid. In deference to the potential epimerization at the α-center under the typical Birch reduction conditions, desulfonylation of **86** was achieved by irradiation in the presence of anisole and ascorbic acid[47] giving **88**.



86



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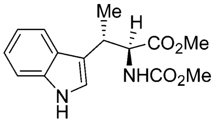
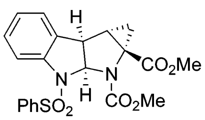


88

Cyclopropanation of **76** was achieved through standard sulfur ylid chemistry in dimethyl sulfoxide at room temperature and **89** was isolated in 56% yield as the only adduct. Reaction of **76** with cyclopentadiene in dichloromethane at reflux gave **90**, again as a single diastereomer, in 71% yield.[43] This highly diastereoselective Diels-Alder reaction, which takes place in the exo-mode with respect to the 2-CO_2Me group, is reminiscent of the exo-selective Diels-Alder reaction of *N*-methoxycarbonyl dehydroalanine methyl ester with cyclopentadiene.[43] While the cyclopropane derivative **89** underwent facile opening to the protected cyclopropatryptophan **91** in 81% yield with trifluoroacetic acid in deuteriochloroform in only 30 min at room temperature, the Diels-Alder adduct **90**, like the *tert*-butyl derivative **81**, was unchanged after several months in neat trifluoroacetic acid.[43]



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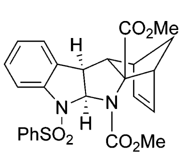
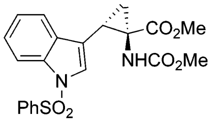


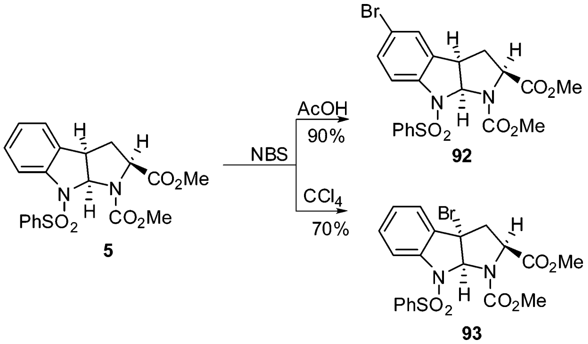
90



91

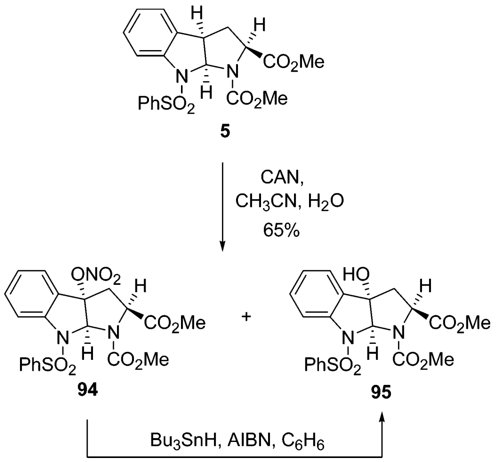
Functionalization at C3a.[48−50] The hexahydro[2,3-*b*]-pyrroloindole skeleton is readily functionalized at the 3a-position by reaction with *N*-bromosuccinimide (NBS) under typical free-radical conditions in tetrachloromethane to give the 3a-bromide in good yield (Scheme 5). On the other hand, exposure to NBS in acetic acid affords the 5-bromohexahydropyrroloindole in excellent yield (Scheme 5). Related work by the Hino laboratory with *N*-chlorosuccinimide led to the formation of 3a- and 5-chlorohexahydropyrroloindoles.[51−53]

Scheme 5. NBS Mediated Bromination

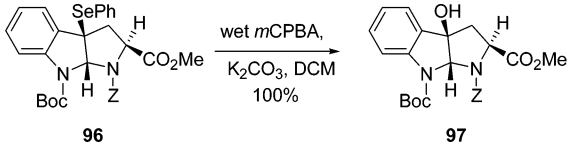


Oxidation of the hexahydropyrroloindole skeleton with ceric ammonium nitrate in wet acetonitrile gave a mixture of the 3a-nitrate and the 3a-hydroxy compounds (Scheme 6). Treatment of this mixture with tributyltin hydride and azoisobutyronitrile, according to the method of Walton and Fraser-Reid,[54] enabled conversion of the nitrate to the alcohol and isolation of a single compound.

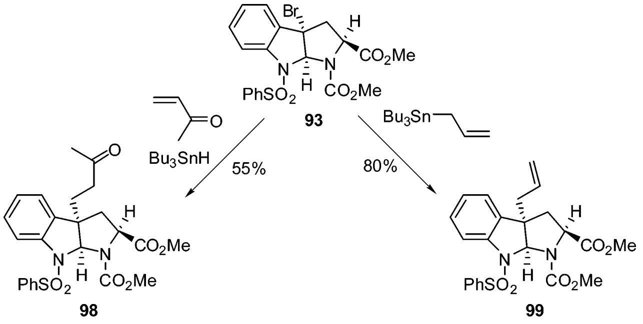
Scheme 6. Benzylic Oxidation with CAN



Scheme 7. Conversion of a 3a-Phenylselenide to a 3a-Hydroxy Compound



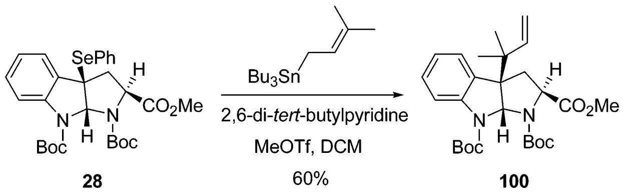
Scheme 8. Radical C—C Bond Formation at the 3a-position



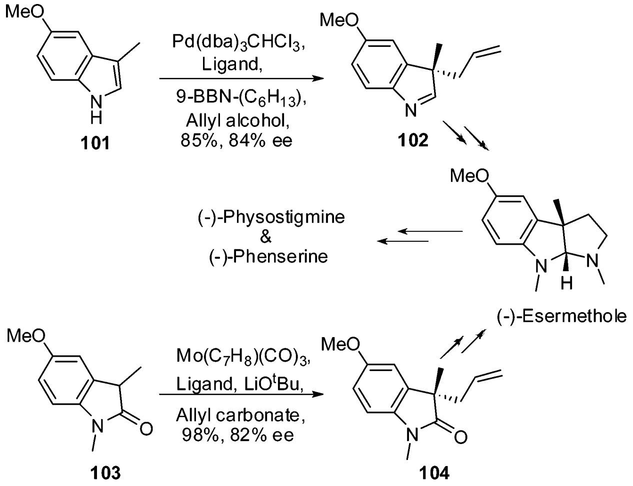
The relative ease with which pyrroloindole **5** can be obtained from tryptophan as a single enantiopure diastereomer on a multigram scale without recourse to chromatography renders these 3a-functionalizations of the intact skeleton competitive with the more classical methods for the formation of related derivatives involving typically unselective cyclizations of tryptophan derivatives with singlet oxygen,[55,56] dimethyl dioxirane,[8] and the like.[57] 3a-Phenylselenides,[9] obtained by cyclization of tryptophan derivatives with selenium-based electrophiles, have been oxidized to the corresponding 3a-hydroxy compounds with wet *m*-chloroperoxybenzoic acid (Scheme 7).[58]

The 3a-bromide and phenylselenides provide convenient handles for the introduction of C—C bonds at the 3a-position. This may be achieved by radical means with tributyltin hydride and an electron-deficient olefin or with allyltributylstannane[9,59] (Scheme 8) or via the 3a-cation on activation of the selenide with methyl triflate (Scheme 9).[9] Not surprisingly, all of these reactions at the 3a-position of the preformed pyrroloindole nucleus afford a single diastereomer that retains the cis-configured ring junction.

Scheme 9. Polar C—C bond Formation at the 3a-Position



Scheme 10. Enantioselective Organocatalytic Synthesis of Tryptamine Derivatives

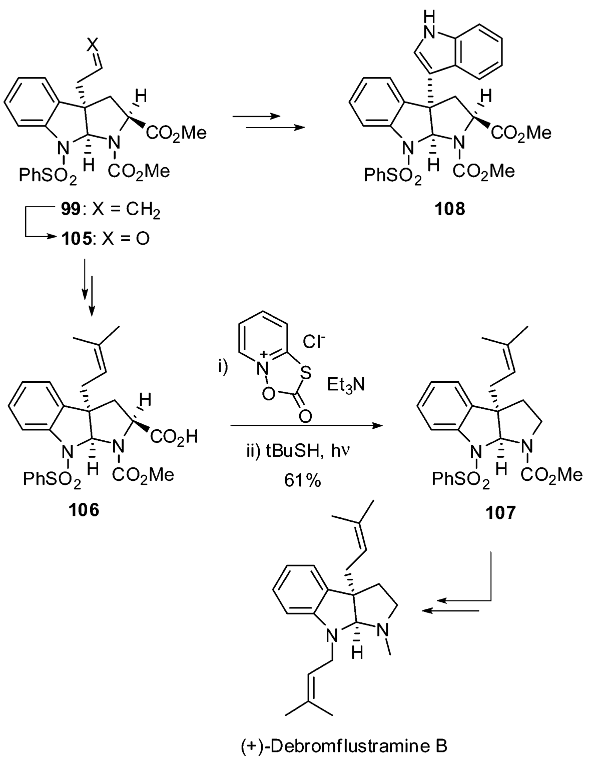


Alternative routes to related 3a-alkyl and allylated hexahydropyrroloindoles include cyclization of tryptophan and tryptamine derivatives with carbon-based electrophiles.[1,60] While direct, such routes have traditionally given only modest yields and racemic products, or mixtures of isomers, starting from tryptamine and tryptophan derivatives, respectively. However, with the advent of organocatalysis, the situation is changing, and it is now possible to achieve the highly enantioselective cyclization of tryptamine derivatives with carbon-based electrophiles in the presence of a suitable catalyst.[61,62] Likewise, palladium-catalyzed asymmetric allylation of tryptamine derivatives or other indoles has recently been shown to be a promising entry into the 3a-allylhexahydropyrroloindoles (Scheme 10).[6,63,64]

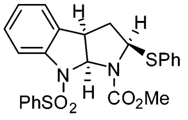
As is readily appreciated, once a C—C bond has been introduced at the 3a-position, it may be further manipulated in the assembly of a variety of hexahydropyrroloindole alkaloids, as in our synthesis of (+)-debromflustramine B (Scheme 11).[49] A key step in this synthesis, and the related synthesis of (+)-pseudophrynaminol,[50] is the ultimate removal of the original, stereodirecting chiral center by means of a Barton decarboxylation reaction.[65] Fischer indolization of the aldehyde **105**, obtained on oxidative cleavage of **99**, with phenylhydrazine provided a direct entry into the core structure (**108**) of leptosins D−F (Scheme 11).[66]

Radical Reactions at C2.[67] In view of the very high degree of exo-selectivity observed in the enolate alkylations and aldol condensations (Table 1, Schemes 3 and 4), it was initially anticipated that the quenching of C2 radicals, generated by Barton decarboxylation of the corresponding acids, would take place with preferential

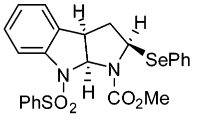
Scheme 11. Synthesis of (+)-Debromoflustramine B and the Leptosin D–F Core Structures



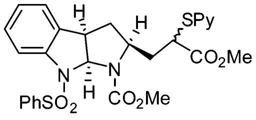
trapping on the exo-surface of the pyrroloindole nucleus.However, this was not the case in practice with the C2-radical typically being quenched in an endo-selective manner. With an unsubstituted C2 radical and a bulky trap such as diphenyl disulfide, or diphenyl diselenide, almost complete selectivity was obtained for reaction on the endo surface, as in the formation of **109** and **110**.[68,69] The stereochemistry of **109** and **110** was readily apparent from the ^{1}H-NMR coupling motifs, which followed the pattern previously established, and was confirmed by X-ray crystallographic analysis of **110**.[68] Radical decarboxylation with trapping by methyl acrylate,[69] leading to the formation of **111**, was also highly endo-selective (13:1).



109



110

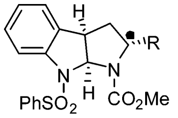


111

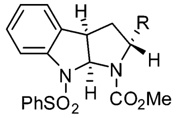
Trapping the C2 alkyl substituted radicals **112**–**114** with *tert*-butylmercaptan gave mixtures of the exo (**115**–**117**) and endo (**118**–**120**) alkyl pyrroloindoles, with the degree of exo-facial trapping increasing with the size of the C2-alkyl group (Table 2).[69] A similar progression was observed with mesitylenethiol as trap.

Table 2. Trapping of C2 Radicals with *tert*-Butylmercaptan

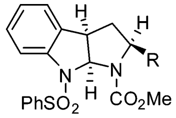
substrate	R	products (% yield)	exo:endo ratio
112	Me	**115** + **118** (69)	1.8:1
113	Et	**116** + **119** (72)	1:1.5
114	^{i}Pr	**117** + **120** (59)	1:1.9



112: R = Me
113: R = Et
114: R = ^{i}Pr



115: R = Me
116: R = Et
117: R = ^{i}Pr



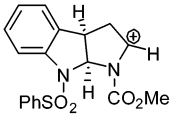
118: R = Me
119: R = Et
120: R = ^{i}Pr

Overall, a trend began to emerge from the radical reactions in which reaction at C2 takes place preferentially on the endo-surface. This endo-facial selectivity is diminished when a pre-existing C2 substituent competes for the endo-position and is progressively eroded as the size of the C2-substituent increases.

Iminium Ions.[68] The isolation of the C2-selenide **110** provided the opportunity to study the reactivity and stereoselectivity of the N-acyliminium type ion **121**. Treatment of **110** or **122** with a suitable Lewis acid ($SnCl_4$) in the presence of a range of nucleophiles resulted in a series of highly endo-selective reactions (Table 3), with confirmation of stereochemistry coming from the familiar ^{1}H-NMR coupling patterns and, in some cases (**123**, **124**, and **126**), X-ray crystallography. Typically, the 2-endo-substituted pyrroloindole product was accompanied by a single enantiomer of the corresponding α-substituted tryptamine, which arose by Lewis acid mediated cycloreversion subsequent to trapping of the iminium ion.

Table 3. Reaction of C2 N-Acyliminium Ions

substrate	nucleophile	product (% yield)
110	$Me_3SiCH_2CH{=}CH_2$	**123** + **124** (37 + 43)
110	$^nBuSnCH_2CH{=}CH_2$	**124** (90)
122	Me_3SiCH_2CCH	**125** (64)
122	Me_3SiCN	**126** (93)



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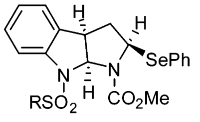
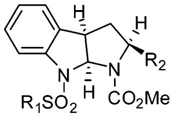
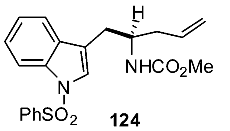


110: R = Ph
122: R = 4-MePh



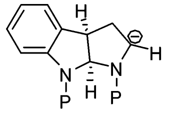
123: R_1 = Ph; R_2 = $CH_2CH{=}CH_2$
125: R_1 = 4-MePh; R_2 = $CH{=}C{=}CH_2$
126: R_1 = 4-MePh; R_2 = CN



124

C2-Enolates: Reconsideration of Stereoselectivity. The endo-facial selectivity observed in the quenching of the C2 radicals and iminium ions provoked a reconsideration of the enolate alkylation and aldolization reactions.[68] Under the emerging paradigm, the observed exo-selectivity of these enolate-based reactions is not due to any inherent exo-facial selectivity in the system. Rather, it is a consequence of the existing C2 substituent (the carboxylate group) out-competing the incoming electrophile for the preferred endo-site. To test this hypothesis, we attempted to generate C2-unsubstituted anion **127** or its pseudoenantiomer from sulfides **109** or **129** or from nitrile

128 under a variety of reducing conditions with the expectation that quenching would occur selectively from the endo-surface. Unfortunately, despite our best efforts, only decomposition products were observed,[70] and it is apparent that anions of the type **127** are not sufficiently long-lived for alkylation to take place.



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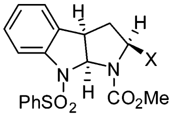
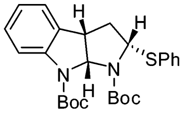


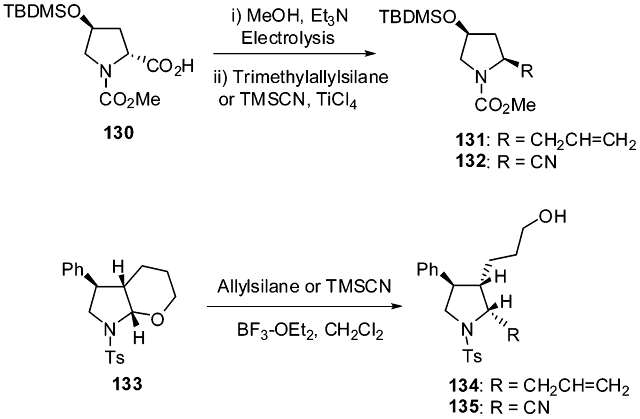
109: X = SPh
128: X = CN



129

A Model for Selectivity at C2. Overall, it is apparent that at C2 of the hexahydropyrroloindole nucleus there is both a kinetic and thermodynamic preference for the endo-position: C2-unsubstituted radicals and cations are quenched selectively from the endo-face, just as under equilibrating conditions the C2-endo-substituted products predominate. In other words, both incipient bonds to C2, at the transition states of reactions at that position, and actual covalent bonds to C2 show a preference for the endo- over the exo-position. As we have previously discussed,[67,68] this endo-preference is due to the minimization of torsional strain around the C-ring in its preferred conformation, augmented by the concomitant minimization of ^{1,3}A-strain between the C2 subsitutent (existing or incoming) and the carbamate N=C partial double bond. When C2 bears an existing substituent, then the selectivity of reactions is diminished and even inverted owing to the competition for the endo-position between the full covalent bond to the existing substituent and the longer, partial bond to the incoming reagent. This reversal of selectivity is complete with the enolate alkylation and aldolization reactions when the existing substituent is the bulky carboxylate and its associated counterion. The analogous reversal of selectivity is seen in the exo-selective formation of **78** from the C2-carbomethoxy N-acyliminium ion **77** when compared to the C2-unsubstituted congeners (Table 3). It seems likely that in the cis-selective attack of nucleophiles on substituted N-carbamoyl[71] and N-sulfonyl[72] derived iminium ions a similar effect is in play, rather than the neighboring group participation originally advanced (Scheme 12).

Scheme 12. N-Carbamoyl and N-Sulfonyl Derived cis-Selective Iminium Ion Quenching



The overall picture closely resembles that developed by Woerpel and co-workers for nucleophilic attack on tetrahydrofuran-derived five-membered cyclic oxacarbenium ions, in which the preferred transition state involves endo-selective attack on an envelop conformation, owing to the minimization of torsional strain.[73,74]

Conclusion

What began as a fortuitously correct exercise on the exo-facial alkylation of hexahydropyrroloindole C2 enolates was ultimately shown to be based on a false premise, with the true preference in most systems, kinetic and thermodynamic, being for the endo-position. The goal-driven development of novel synthetic methodology was revealed yet again to be a fertile ground for the development of a deeper understanding of the science of organic chemistry.

D. C. thanks the numerous colleagues, co-workers, and collaborators, whose names can be found in the references below, for their many intellectual and practical contributions to this project.

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