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Endo-Selective Quenching of Hexahydropyrrolo[2,3-*b*]indole-Based *N*-Acyliminium Ions

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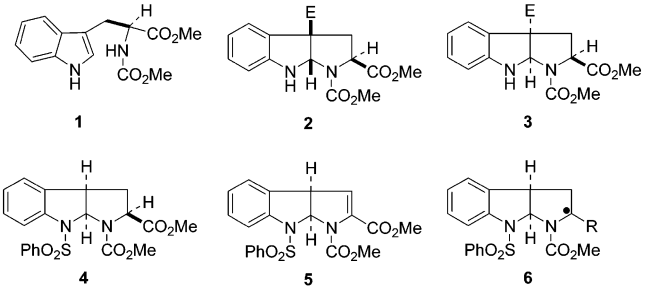
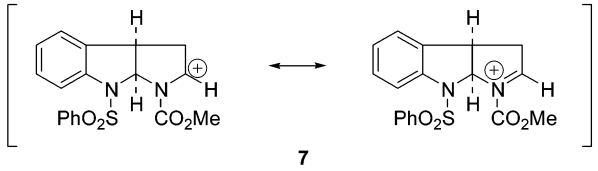
Received February 11, 2004

Abstract: Radical decarboxylation of L-tryptophan-derived (2*S*,3a*R*,8a*S*)-8-arylsulfonyl-1,2-di(methoxycarbonyl)-1,2,3,-3a,8,8a-hexahydro-2*H*-pyrrolo[2,3-*b*]indoles **8** and **9** in the presence of diphenyl diselenide results in the endo-selective formation of (2*R*,3a*R*,8a*S*)-8-arylsulfonyl-1-methoxycarbonyl-2-phenylselenyl-1,2,3,3a,8,8a-hexahydro-2*H*-pyrrolo[2,3-*b*]indoles **10** and **11**. These selenides, in conjunction with Lewis acids, serves as precursors to the corresponding *N*-acyl iminium ions, which undego selective endo-face quenching by allyltributylstannane, allyltrimethylsilane, propargyltrimethylsilane, and trimethylsilylcyanide. Stereochemical assignments rest on NMR data and crystallographic studies. The endo-selective nature of these reactions is interpreted in terms of minimization of allylic strain at the transition state for nucleophilic attack on the *N*-acyl iminum ion.

The chemistry of the 2-substituted hexahydropyrrolo-[2,3-*b*]indole tautomers **2** and **3** of tryptophan continues to be of considerable importance owing (i) to the application of this system in the synthesis of numerous alkaloids of diverse biological activity,[1−8] (ii) to their use as templates for the stereocontrolled formation of tryptophan analogues,[9−15] and (iii) the intriguing enigma of the kinetic and thermodymanic stereoselectivity at the 2-position.[16−21] With respect to the question of stereoselectivity at the 2-position, treatment of tryptophan derivatives **1** with electrophiles (E^+), typically strong acids or organoselenium-based electrophiles, leads to the formation of the kinetic exo-substituted hexahydropyrrolindole **2**, which rapidly equilibrates to the endo-isomer **3**.[4,18,20,22] Irreversible cyclizations, typically those mediated by oxygen-based electrophiles,[8,21,23,24] give mixtures of exo- and endo-substituted hexahydropyrroloindoles.[8,21] Deprotonation of **4**, a stabilized form of **3**, and alkylation of the resultant enolate takes place with retention of configuration, i.e., with high kinetic selectivity for the exo-face.[10] Conjugate additions, and cycloadditions to the tetrahydro system **5**, likewise take place with excellent exo-face selectivity.[13] Generation of radical **6** and quenching with a variety of traps, however, results in preferential formation of the endo-trapped product, with endo-selectivity increasing with the size of the trap.[19]



This background, together with the generally useful chemistry of *N*-acyl iminium ions[25] and the current interest in the endo-face selective quenching of related fused bicyclic five-membered oxocarbenium ions,[26] prompted a study of the generation and trapping of cationic species **7** at the 2-position of the hexahydropyrrolo[2,3-*b*]indole framework which we report here.



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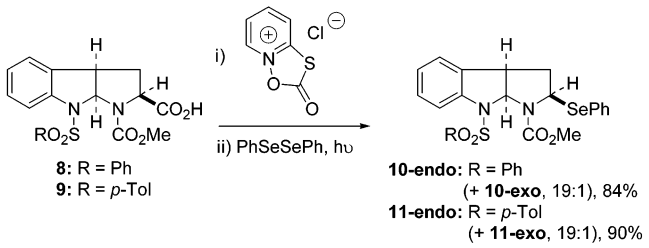
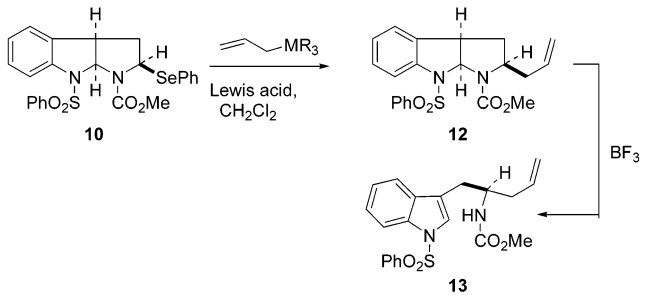
10.1021/jo049757p CCC: $27.50
Published on Web 04/24/2004

SCHEME 1



SCHEME 2



An appropriate cation precursor, selenide **10**, was obtained in 84% yield as a 19:1 endo/exo mixture by Barton decarboxylation[27,28] of acid **8**[19] in the presence of diphenyl diselenide.[29] The endo-selectivity in this radical reaction exactly mirrors that observed previously on quenching of the same radical with diphenyl disulfide.[19] The relative stereochemistry of **10**-*endo* was assigned on the basis of the $^3J = 0$ value of the H-2−H-3-endo coupling, which has been previously shown[10,16−18] to be diagnostic for the 2-endo-substituted series in the preferred conformation with C-2 puckered in toward the concave face of the tricyclic system so as to minimize ^{1,3}A strain about the N−C carbamate partial double bond. X-ray crystallographic analysis of **10**-*endo* fully confirms this assignment.[30] As expected the *p*-toluenesulfonyl analogue **9** of **8** performed exactly analogously affording the crystalline *endo*-selenide **11** (Scheme 1), which was also X-ray characterized.

With a suitable, stable precursor in hand, attention was turned to the *N*-acyl iminium ion chemistry. Reaction of **10**-*endo* with allyltrimethylsilane in the presence of a range of Lewis acids resulted in the formation of two products, the *endo*-allyl product **12** and the allyltryptamine derivative **13** (Scheme 2) with the yields and ratios recorded in Table 1. Analogous observations were made with allyltributylstannane. The configuration of **12**, initially assigned on the basis of a ROESY interaction between H-2exo and H3a, was unambiguously determined by single-crystal X-ray crystallographic analysis. The possibility arose that the initial quenching of the *N*-acyl iminium ion was poorly selective giving rise to **12** in a mixture with its exo isomer and that, under the Lewis acid conditions of the reaction, the less stable[16] exo-isomer was undergoing ring opening to the tryptamine derivative. However, when a purified sample of **12** was exposed to BF_3 at room temperature it was converted to **13** whose specific rotation matched, in sign and magnitude, that of the sample isolated from the allylation reaction. Tryptamine **13** therefore has the absolute configuration indicated in Scheme 2 and arises from slow opening of the endo-product **12**, with the relative proportions of **12** and **13** (see Table 1) depending on the reaction conditions.[31] This result, of course, leads to the conclusion that the quenching of cation **7** by allyltrimethylsilane and allytributylstannane is very highly endo-selective.

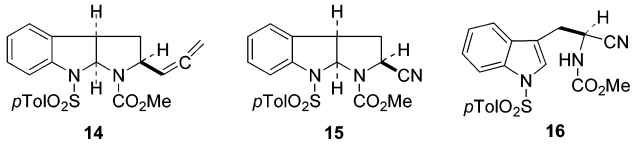
TABLE 1. Diastereoselective Reactions of 10-*endo* with Allyltrimethylsilane and Allyltributyltin in the Presence of Lewis Acids

entry	nucleophile	Lewis acid	reaction time (h)	temp (°C)	**12/13** (%)	yield (%)
1	$(CH_3)_3SiCH_2CH{=}CH_2$	$SnCl_4$	1.5	−30	46:54	80
2	$(CH_3)_3SiCH_2CH{=}CH_2$	BF_3	1.5	0	75:25	70
3	$(CH_3)_3SiCH_2CH{=}CH_2$	$TiCl_4$	5	25	32:68	55
4	$^nBu_3SnCH_2CH{=}CH_2$	$SnCl_4$	1.5	−30	0:1	90
5	$^nBu_3SnCH_2CH{=}CH_2$	BF_3	1.5	0	76:24	78
6	$^nBu_3SnCH_2CH{=}CH_2$	$TiCl_4$	3	25	24:76	43

TABLE 2. Diastereoselective Reactions of 11-*endo* with Propargyltrimethylsilane and Trimethylsilyl Cyanide in the Presence of Lewis Acids

entry	nucleophile	Lewis acid	reaction time (h)	temp (°C)	product	yield (%)
1	$(CH_3)_3SiCH_2CCH$	$SnCl_4$	1.5	−30	**14**	64
2	$(CH_3)_3SiCH_2CCH$	BF_3	1.5	0	**14**	53
3	$(CH_3)_3SiCH_2CCH$	$TiCl_4$	4	25	**14**	23
4	$(CH_3)_3SiCN$	$SnCl_4$	1.5	−30	**15**	93
5	$(CH_3)_3SiCN$	BF_3	1.5	0	**16**	57
6	$(CH_3)_3SiCN$	$TiCl_4$	8	25	**15**	49

Condensation of selenide **11** with propargyltrimethylsilane and trimethylsilylcyanide followed the pattern established with the allylmetal nucleophiles with extremely high selectivity for the formation of the endo-product **14** and **15**, respectively (Table 2). In the case of trimethylsilylcyanide the ring-opened product **16** was isolated when BF_3 etherate was employed as Lewis acid.



The relative stereochemistry of the allene **14** was assigned on the basis of an interaction between H-2exo and H-3a in the ROESY spectrum whereas the corresponding interaction in the NOESY spectrum of **15** confirmed the endo-nature of the cyano group. The

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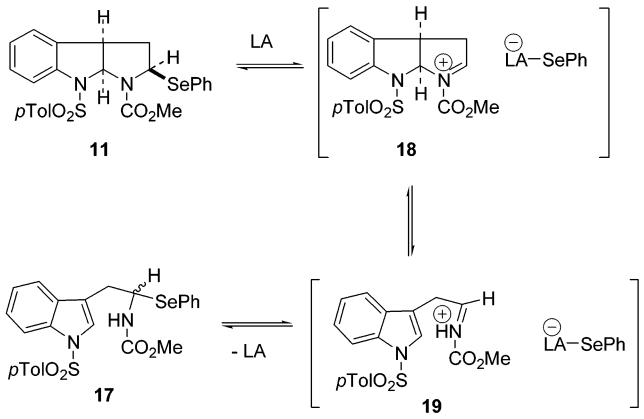
(30) The absolute configuration for chiral C-atoms was unambiguously determined as 2*R*,3a*S*,8a*S* and the carbamate partial double bond is reflected in the short distance N1−C9, 1.369(4) Å.

(31) The proposed configuration was further confirmed by an X-ray analysis of **13**. It is worth mentioning that **13** crystallizes with two independent molecules in the asymmetric unit, reflecting a degree of free rotation for SO_2Ph moiety along the N8−S1 bond. On the other hand, the formation of a double bond during the ring opening is confirmed by bond lengths C3a−C8a = 1.333(6) and 1.345(6) Å for the first and second molecule, respectively.

SCHEME 3



relative configuration of **15** was also confirmed by single-crystal X-ray analysis.[32] The absolute configuration of the ring-opened cyanide **16** is assigned by analogy with the absolute configuration of tryptamine **13**.

When **11** was activated with $SnCl_4$, $BF_3{\cdot}OEt_2$, and $TiCl_4$ in the presence of vinyltrimethylsilane and trimethylsilylacetylene no substitution was observed. In these cases the only product isolated was the ring-opened racemic selenide **17**, whose structure was also confirmed crystallographically. Presumably, the formation of **17** arises from ring opening of the initial *N*-acyl iminium ion **18** in competition with capture by the less nucleophilic vinyl and acetylenyl silanes. The ring-opened *N*-acyl iminium ions are then quenched from either face by the selenide−Lewis acid complex leading to the formation of racemic **17** (Scheme 3). This sequence is in line with the X-ray study of **17**: in contrast with previous compounds, **17** crystallizes in a center-symmetric space group, in agreement with a racemic configuration at C2. Moreover, as for **13**, the double bond formed during the ring opening is characterized by the expected bond length, C3a−C8a = 1.349(8) Å.

Although the nucleophilic capture of **7** and its tosyl analogue **18** has only been achieved with a limited range of nucleophiles because of an apparent competition with the ring opening illustrated in Scheme 3, it is evident that when capture does take place it occurs with high selectivity from the endo-face of the tricyclic system. Thus, the stereoselective nucleophilic capture of C-2 cation parallels that of the quenching of C-2 radicals but opposes that of the exo-selective alkylation of C-2 enolates. We believe that the stereoselectivity of all three processes is dominated by the need to minimize ^{1,3}A strain between the substituents at C-2 and the carbamate N=C partial double bond. At the same time torsional strain around the terminal ring is better minimized when attack takes place from the endo-face rather than the exo-face of the system. This argument is best appreciated by examination of the conformation of the ester **4**, which is well-established to be the thermodynamic isomer. In the preferred endo-isomer of **4** computational[16] and crystallographic studies[17,33] show the terminal pyrrolidine ring to be in an envelope-like conformation with C-2 puckered in toward the endo face of the molecule. In this conformation the C-2 endo substituent is perpendicular to the plane of the carbamate, thereby minimizing ^{1,3}A strain, and torsional interactions around the ring are minimized. This same conformation is evident in the X-ray crystallographic structures of compounds **10** and **12**, as presented here. It seems entirely reasonable then that the approach of nucleophiles to cations **7** and **18** as well as of radical traps to radical **6** will take place from the direction that engenders minimal ^{1,3}A strain in the developing bond, i.e., from the endo face. In the alkylation of the enolate of **4**, however, there is a competition for the favored endo position between the existing C-2−CO_2-Me bond and the incipient bond to the incoming electrophile. At the transition state, the need to minimize ^{1,3}A strain to the existing C−C bond is obviously greater than that to a partial bond resulting in the observed exo-selective alkylations.[34]

Acknowledgment. We thank CONACyT (Project No. 35102-E and Grant No. 91277) for financial support of this work.

Supporting Information Available: Complete experimental details, copies of the ^{1}H and ^{13}C NMR spectra for compounds **10**−**17**, and X-ray crystallographic details for compounds **10**−**13**, **15**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) The cyano group is characterized by a formal triple bond, C13−N14 = 1.127 (5) Å; the configuration for C3a and C8a remains unchanged relative to starting material, while the C2 atom presents now an *S* configuration.

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(34) In the possibly related cis-selective attack of nucleophiles on substituted *N*-carbamoyl[35] and *N*-sulfonyl[36] pyrrolidine derived iminium ions, neighboring group participation from the carbamoyl or sulfonyl group has been invoked as a possible explanation for the stereoselectivity. While this may be possible with the *N*-sufonyl system, with the tetrahedral sulfur and longer N−S and S−O bonds, it seems unlikely in *N*-carbamoyl systems, such as those described here, when it would require the disruption of the crystallographically well-established N=C(O$^-$)OMe double bond character.

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