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Intramolecular Conjugate Displacement: A General Route to Hexahydroquinolizines, Hexahydroindolizines, and Related [*m*,*n*,0]-Bicyclic Structures with Nitrogen at a Bridgehead

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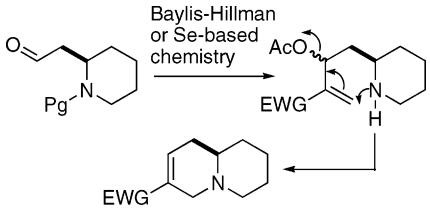
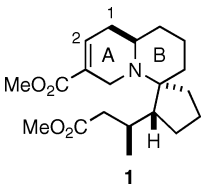


N-Protected amino aldehydes can be converted into allylic alcohols by the classical Morita−Baylis−Hillman reaction (cf. **2** → **3**) or by condensation with selenium-stabilized carbanions, followed by oxidation (cf. **2** → **8** → **3**). The derived acetates undergo cyclization when the nitrogen protecting group is removed, affording [*m*,*n*,0]-bicyclic structures with nitrogen at a bridgehead (cf. **4** → **5** → **6**). Formation of bicyclic structures via the reactions of Schemes 1 and 2 is general, and the stereochemistry of the starting amino aldehyde is preserved.

Introduction

During work directed at the total synthesis of the marine alkaloid halichlorine, a stage was reached where it was necessary to generate ring A of compound **1** from a precursor in which



1

C(1) and C(2) were initially part of a linear substituent on ring B.[1] This was achieved[1] by a short sequence that constitutes a new and general method for making [*m*,*n*,0]-bicyclic structures with nitrogen at a bridgehead; such heterocyclic structures are subunits of many alkaloids,[2−4]including substances with important biological properties.[4] Our approach,[1,5]which is summarized in Scheme 1for a generic case with six-membered rings, is based on formation of Morita−Baylis−Hillman (MBH) alcohols[6] (**2** → **3**) and their derivatization as acetates (**3** → **4**), followed by a type of ring closure (**4** → **5** → **6**) that resembles both a Michael addition and an S_N2' displacement. We suggest the name "intramolecular conjugate displacement" (ICD) for such processes.[7]

We describe here full details of this general method, as well as a route (Scheme 2) to MBH alcohols that is based on selenides **7**; the latter route works even in cases where the classical MBH procedure fails or is very slow.

Results and Discussion

Preparation of Starting Aldehydes for the Classical Morita−Baylis−Hillman Reaction. The essential starting

(1) Preliminary communication: Clive, D. L. J.; Yu, M.; Li, Z. *Chem. Commun.* **2005**, 906−908.

(2) Indolizidine and quinolizidine alkaloids: Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 719−741.

(3) For a recent new approach to quinolizidines, see: Maloney, K. M.; Danheiser, R. L. *Org. Lett.* **2005**, *7*, 3115−3118.

(4) (a) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids*: *Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: New York, 1999; Vol. 13, pp 1−161. (b) Michael, J. P. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 2001; Vol. 55, pp 91−258.

(5) (a) For a mechanistically related (and earlier) approach to the halichlorine system, see: Christie, H. S.; Heathcock, C. H. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12079−12084. (b) A variant of our approach has been used in a formal synthesis of halichlorine: Andrade, R. B.; Martin, S. F. *Org. Lett.* **2005**, *7*, 5733−5735.

(6) Reviews on the Morita−Baylis−Hillman reaction: (a) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653−4670. (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8011−8062. (c) Ciganek, E. *Org. React.* **1997**, *51*, 201−350. (d) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811−891.

(7) For speculation on the mechanism of related *intermolecular* processes, see: Knochel, P.; Seebach, D. *Tetrahedron Lett.* **1981**, *22*, 3223−3226.

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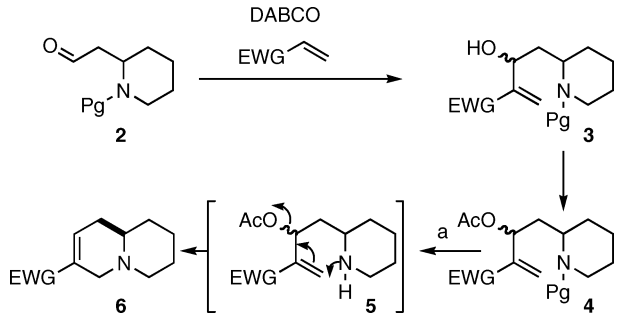
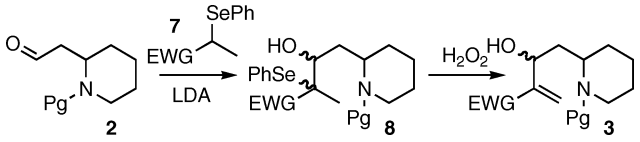
SCHEME 1[a]



[a] Pg = protecting Group, EWG = electron-withdrawing group, a = deprotection of nitrogen.

SCHEME 2[a]



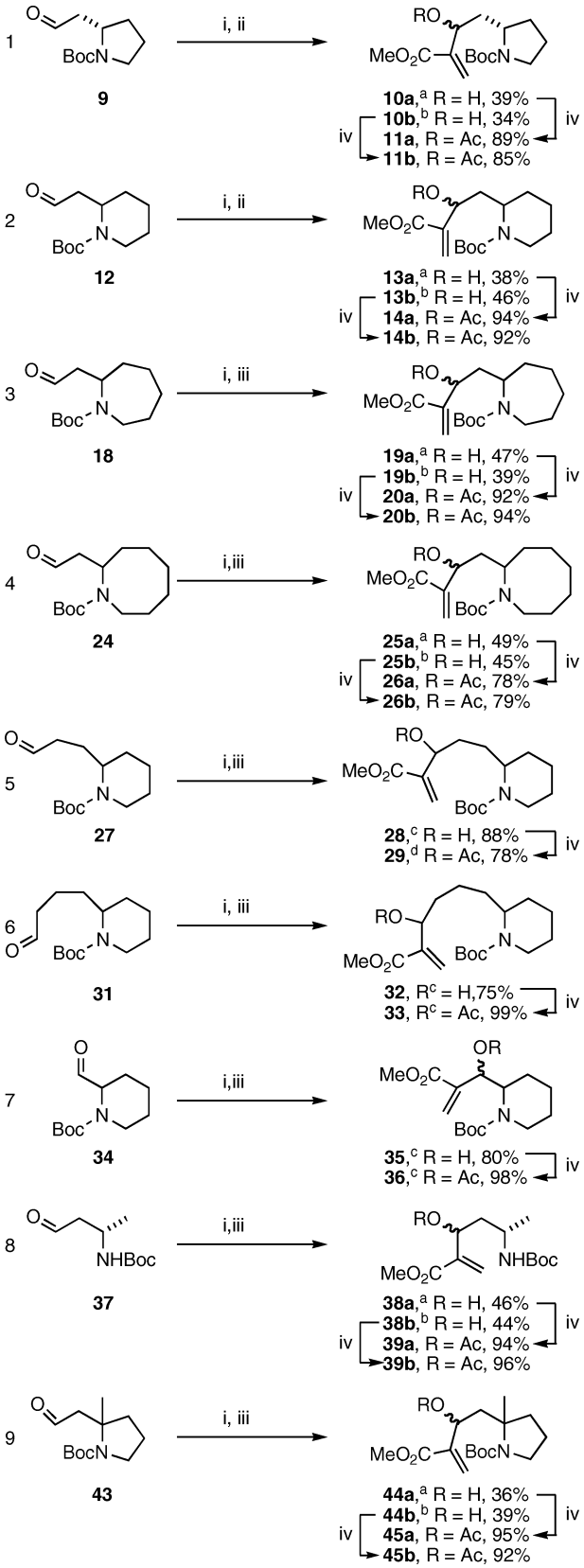
[a] Pg = protecting Group, EWG = electron-withdrawing group.

materials are *N*-protected amino aldehydes (cf. **2**); most of those used in the present research are shown in Table 1, and they are all readily accessible. Optically pure **9**[8] was made[9−11]from *N*-Boc-(*S*)-proline by carboxyl reduction (B_2H_6),[9] Parikh-Doering oxidation ($-CH_2OH \rightarrow -CHO$),[9] Wittig olefination with $Ph_3P{=}CHOMe$ [$-CHO \rightarrow -CH{=}CH(OMe)$],[10,12]and enol ether hydrolysis[10] [$Hg(OAc)_2$, KI]. This Wittig homologation process worked in all cases we tried, except where the formyl group was attached directly to a four-membered ring (2-formylazetidine-1-carboxylic acid *tert*-butyl ester[13]); in this case the ring opened during the homologation, possibly by silica-induced hydrolysis of the intermediate enol ethers.

Commercial (2-hydroxyethyl)piperidine was converted by *N*-protection (Boc_2O, Et_3N) and Dess−Martin oxidation into aldehyde **12**.[14]

The new aldehyde **18** was made as summarized in Scheme 3.[15,16] Application of the Schmidt reaction to ketone **15** generated lactam **16**,[15]and this was reduced ($LiAlH_4$) to amino alcohol **17**,[15,16] which was then protected on nitrogen by reaction with Boc_2O[16]and oxidized under Swern conditions (**17** → **18**).

TABLE 1. Formation of Morita−Baylis−Hillman Adducts[e]



[a] More polar alcohol. [b] Less polar alcohol. [c] We did not establish if the material is a mixture of isomers or a mixture of rotamers of a single isomer. [d] Appears to be a single isomer (^{13}C and ^1H NMR). [e] Reagents and conditions: (i) methyl acrylate, DABCO; (ii) 3 days; (iii) 5 days; (iv) AcCl, pyridine, CH_2Cl_2.

(8) Toujas, J.-L.; Jost, E.; Vaultier, M. *Bull. Soc. Chim. Fr.* **1997**, *134*, 713−717.

(9) Pettit, G. R.; Singh, S. B.; Herald, D. L.; Lloyd-Williams, P.; Kantoci, D.; Burkett, D. D.; Barkóczy, J.; Hogan, F.; Wardlaw, T. R. *J. Org. Chem.* **1994**, *59*, 6287−6295.

(10) Cf.: Ansell, M. F.; Caton, M. P. L.; Stuttle, K. A. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1069−1077.

(11) Cf.: Ikeda, M.; Shikaura, J.; Maekawa, N.; Daibuzono, K.; Teranishi, H.; Teraoka, Y.; Oda, N.; Ishibashi, H. *Heterocycles* **1999**, 31−34.

(12) Racemic enol ethers: Calvet, A. P.; Jacobelli, H.; Junien, J.-L.; Riviere, P.; Roman, F. J. PCT Int. Appl. WO 9515948 A1, 1995.

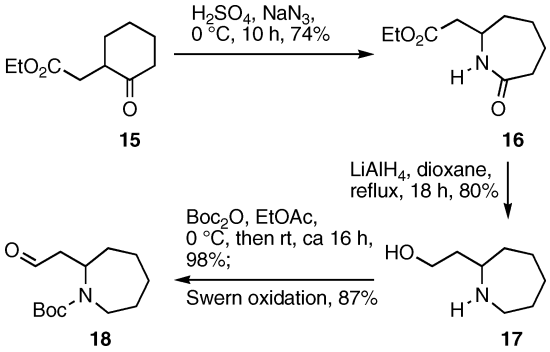
(13) Balboni, G.; Marastoni, M.; Merighi, S.; Borea, P. A.; Tomatis, R. *Eur. J. Med. Chem.* **2000**, *35*, 979−988.

(14) Cf.: (a) Rouden, J.; Seitz, T.; Lemoucheux, L.; Lasne, M.-C. *J. Org. Chem.* **2004**, *69*, 3787−3793. (b) Ikeda, M.; Kugo, Y.; Sato, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1819−1824.

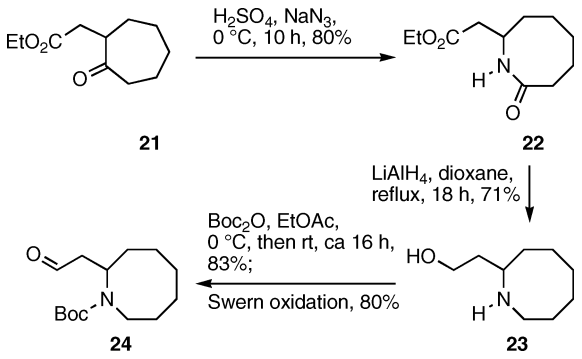
(15) Psiorz, M.; Heider, J.; Bomhard, A.; Reiffen, M.; Hauel, N.; Noll, K.; Narr, B.; Lillie, C.; Kobinger, W.; Dammgen, J. U.S. Patent 5,175,157, 1992.

(16) Cf.: DeVita, R. J.; Goulet, M. T.; Wyvratt, M. J.; Fisher, M. H.; Lo, J.-L.; Yang, Y. T.; Cheng, K.; Smith, R. G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2621.

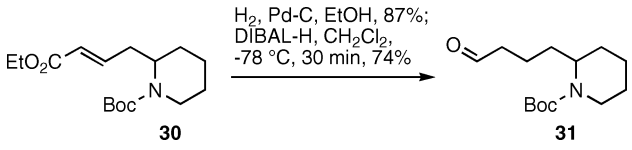
SCHEME 3



SCHEME 4



SCHEME 5



The next homolog (**24**) was obtained (Scheme 4) by applying the same sequence of reactions to **21**.[17]

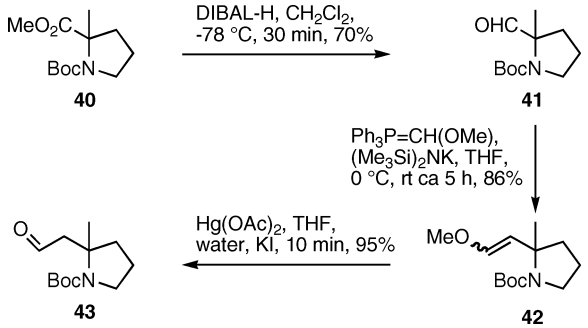
The reported method was used to make aldehyde **27**,[18]except that the formyl group was generated by DIBAL-H reduction of the corresponding ethyl ester, rather than by $LiAlH_4$ reduction and Swern oxidation.

Hydrogenation and DIBAL-H reduction of the known ester **30**[19] (Scheme 5) provided aldehyde **31**.[20]

Aldehyde **34**[18] was made as reported, and the known compound **37**[21] was obtained from *N*-Boc-(L)-alanine by a 3-step literature procedure.[21]

Finally, the angularly methylated compound **43** was also prepared by Wittig homologation of the appropriate aldehyde

SCHEME 6



(Scheme 6), starting from racemic ester **40**,[22]which was made by methylation (LDA, MeI) of *N*-Boc-(*S*)-proline methyl ester.[23]

Formation of Morita−Baylis−Hillman Adducts. Each of the aldehydes shown in Table 1 was stirred for several days in methyl acrylate in the presence of DABCO; condensation occurred smoothly under these conditions to afford the expected alcohols in good yield (73−94%). In most cases a separable mixture of alcohols epimeric at the hydroxyl-bearing carbon was obtained. Each of the alcohols was readily acetylated by AcCl in the presence of pyridine, and again the yields are high. On the basis of one experiment, use of Ac_2O in pyridine appeared to be unsatisfactory.

Formation of Bicyclic and Monocyclic Amines from Morita−Baylis−Hillman Acetates. The 6-*endo* cyclization **5** → **6** (Scheme 1) is the crucial step of our sequence.[24] While *O*-acetates of MBH alcohols are well-known to undergo intermolecular S_N2' displacement,[6d,25]the intramolecular 6-*endo* pathway requires that it be faster than *O* → *N* acetyl transfer or direct cyclization onto the electron-withdrawing group (see **5**) when that is an ester[26] or other group susceptible to nucleophilic attack. In the event, these conditions are met in all but one of the examples (i.e., entry 7 of Table 2) we have examined.

Each of the acetates shown in Table 2 was exposed to the action of CF_3CO_2H, initially at 0 °C and then at room temperature. The product was dissolved in MeCN and the solution was stirred for 30 min with 20% aqueous Na_2CO_3 solution. In all cases, except that of entry 7, it was then possible to isolate the desired bicyclic amine, often in more than 90% yield.

(17) Sinclair, I. W.; Proctor, G. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2485−2488.

(18) Sato, T.; Yamazaki, T.; Nakanishi, Y.; Uenishi, J.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1438−1443.

(19) Bustos, F.; Gorgojo, J. M.; Suero, R.; Aurrecoechea, J. M. *Tetrahedron* **2002**, *58*, 6837−6842.

(20) Costanzo, M. J.; Maryanoff, B. E. U.S. Patent 5,523,308, 1996. Our sample of **31** had the following: FTIR (CH_2Cl_2 cast) 1725, 1686 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.32−1.41 (m, 2 H), 1.44 (s, 9 H), 1.47−1.66 (m, 7 H), 1.66−1.80 (m, 1 H), 2.38−2.55 (m, 2 H), 2.72 (t, J = 13.1 Hz, 1 H), 3.96 (br s, 1 H), 4.22 (br s, 1 H), 9.74 (d, J = 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$125 MHz) δ 19.0 (t), 21.5 (t), 25.6 (t), 28.5 (q), 29.0 (t), 33.5 (t), 43.6 (t), 79.3 (s), 155.2 (s), 202.4 (d); exact mass *m*/*z* calcd for $C_{14}H_{25}NNaO_3$ (M + Na) 278.17266, found 278.17267.

(21) McIntosh, J. M.; Acquaah, S. O. *Can. J. Chem.* **1988**, *66*, 1752−1756.

(22) (a) Racemic ester **40** has been reported: Baldwin, J. J.; McDonald, E.; Moriarty, K. J.; Sarko, C. R.; Machinaga, N.; Nakayama, A.; Chiba, J.; Iimura, S.; Yoneda, Y. PCT Int. Appl. WO 2001000206 A1, 2001. (b) Optically pure ester: Lewis, A.; Wilkie, J.; Rutherford, T. J.; Gani, D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3777−3793.

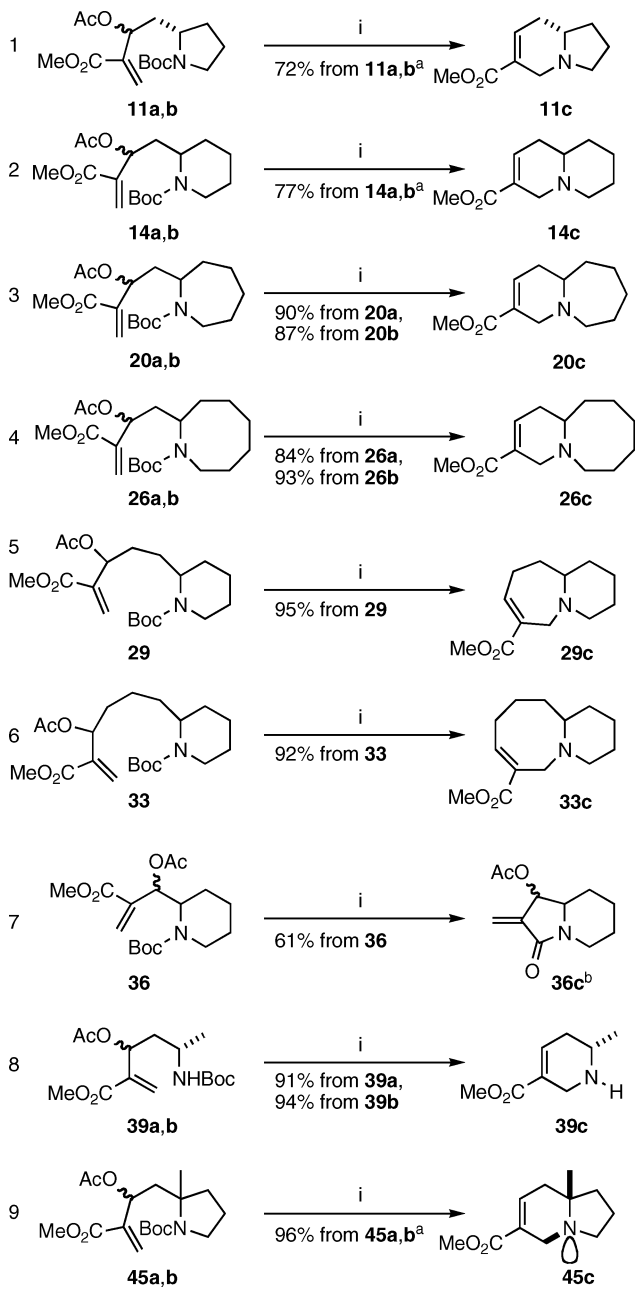
(23) Confalone, P. N.; Huie, E. M.; Ko, S. S.; Cole, G. M. *J. Org. Chem.* **1988**, *53*, 482−487.

(24) Cf.: Bode, M. L.; Kaye, P. T. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1809−1813.

(25) E.g.: (a) Cho, C.-W.; Kong, J.-R.; Krische, M. J. *Org. Lett.* **2004**, *6*, 1337−1339. (b) Nilov, D.; Rächer, R.; Reiser, O. *Synthesis* **2002**, 2232−2242. (c) For sequential inter- and intramolecular S_N2' displacement (analogous to **5** → **6**) to form macrocycles, see: Bauchat, P.; Le Bras, N.; Rigal, L.; Foucaud, A. *Tetrahedron* **1994**, *50*, 7815−7826. (d) Charette, A. B.; Janes, M. K.; Boezio, A. A. *J. Org. Chem.* **2001**, *66*, 2178−2180. (e) For synthons related to the acetates of MBH alcohols, see, for example: (i) Brocchini, S. J.; Eberle, M.; Lawton, R. G. *J. Am. Chem. Soc.* **1988**, *110*, 5211−5212 and references therein. (ii) Seebach, D.; Knochel, P. *Helv. Chim. Acta* **1984**, *67*, 261−283. (iii) El-Awa, A.; Fuchs, P. *Org. Lett.* **2006**, *8*, 2905−2908.

(26) For examples of closure onto an ester: (a) Basavaiah, D.; Reddy, R. M.; Kumaragurubaran, N.; Sharada, D. S. *Tetrahedron* **2002**, *58*, 3693−3697. (b) Cf.: Familoni, O. B.; Kaye, P. T.; Klaas, P. J. *Chem. Commun.* **1998**, 2563−2564. (c) For a related case, where such closure onto an ester does not occur: O'Dell, D. K.; Nicholas, K. M. *J. Org. Chem.* **2003**, *68*, 6427−6430.

TABLE 2. Intramolecular Conjugate Displacements[c]



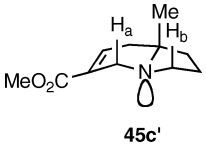
[a] Acetate epimers were used as a mixture. [b] A single isomer (^{13}C and ^{1}H NMR). [c] Reagents and conditions: (i) CF_3CO_2H, CH_2Cl_2, 0 °C to room temperature; then aq Na_2CO_3, 30 min.

The acetates **11a** and **11b**, which were derived from L-proline, gave **11c** with an ee of 99.8% (from a mixture of **11a** and **11b**), establishing the important point that the stereochemistry α to the nitrogen is preserved throughout the sequence. In such cases there is, in principle, the possibility of retro-Michael reaction during the initial Baylis−Hillman condensation, followed by readdition, but this, evidently, does not occur.

The apparent facility of the first few ring closures we studied prompted us to examine acetate **36** (entry 7); it represents a demanding test, as the desired pathway is predicted by the Baldwin rules to be disfavored. In the event, the stereoelectronic factors on which the rules are based are sufficient to divert the pathway away from the desired mode, and closure onto the methyl ester carbonyl occurs; this is clearly the major pathway (61% yield), and we did not search for products of *O* → *N* acetyl transfer.

The examples shown in Table 2 establish that the nitrogen can originally be in a ring of 5−8 atoms, and rings of 6−8 atoms (but not 5) can be formed by the intramolecular conjugate displacement. Entries 5 and 6 of Table 2 show that the intramolecular conjugate displacement pathway leading to 7- and 8-membered rings is preferred over direct S_N2 displacement of acetate, which would have generated 5- and 6-membered rings, respectively.[7] The reaction can also be used to make monocyclic amines; in the single case examined (Table 2, entry 8) the product **39c** was obtained as a single enantiomer, as judged by the ^{1}H NMR spectrum of the derived Mosher amide.

Compound **45c** probably adopts the conformation shown in **45c′** with transoid ring fusion, on the basis of NOE enhancements of the signals representing H_a and H_b, on irradiation of the angular methyl group signal.



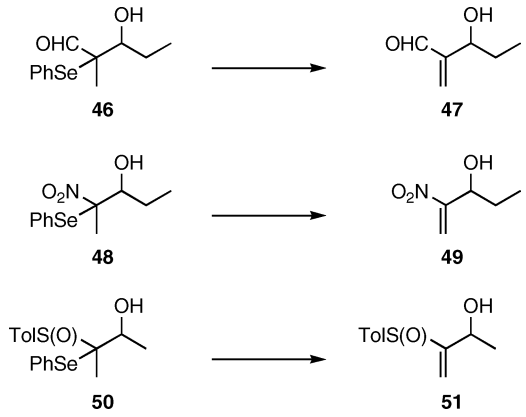
45c'

Selenide Route to Morita−Baylis−Hillman Alcohols. All of the examples listed in Table 2 are based on the use of methyl acrylate. Other olefins can be used in the MBH condensation,[6] but sometimes, depending on the nature of the electron-withdrawing group and the degree of substitution of the double bond, the normal condensation is unacceptably slow or does not work at all.[6] For example, phenyl vinyl sulfone is reported to react very slowly,[27−29]as does methyl crotonate.[29] The process summarized in Scheme 2 was used to deal with such cases. This very simple reaction sequence does not appear to have been fully appreciated as a effective general route to MBH alcohols, in spite of the fact that elimination of selenides *away* from a hydroxyl-bearing carbon (cf. **8** → **3**) has been known for a long time.[30] In the event, the process of Scheme 2 gives ready access to MBH-like alcohols including members of this class that are not accessible by the classical MBH procedure.

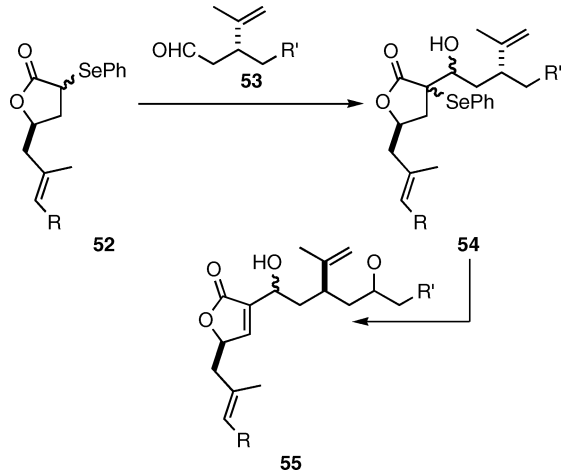
Compounds such as **46**,[31] **48**,[32] and **50**[33] (Scheme 7) have been reported, as well as their transformation into the MBH-like alcohols **47**, **49**, and **51**, respectively, but in all these cases the starting selenides were not made by addition of a selenium-stabilized carbanion to an aldehyde (cf. Scheme 2, **2** → **8**); instead, they were synthesized by attachment of the PhSe group to the complete preformed carbon skeleton. Examples of the condensation of α-(phenylseleno)esters with aldehydes, in which

(27) Weichert, A.; Hoffmann, H. M. R. *J. Org. Chem.* **1991**, *56*, 4098−4112.
(28) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron* **1988**, *44*, 6095−6106.
(29) Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 692−700.
(30) (a) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697−2699. Review: (b) Clive, D. L. J. *Tetrahedron* **1978**, *34*, 1049−1132.
(31) Huot, J.-F.; Outurquin, F.; Paulmier, C. *Chem. Lett.* **1991**, 1599−1991.
(32) Seebach, D.; Calderari, G.; Knochel, P. *Tetrahedron* **1985**, *41*, 4861−4872.
(33) Mase, N.; Watanabe, Y.; Toru, T.; Kakumoto, T.; Hagiwara, T. *J. Org. Chem.* **2000**, *65*, 7083−7090.

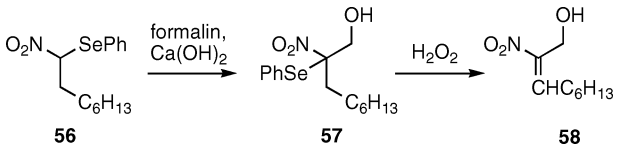
SCHEME 7



SCHEME 8

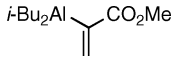


SCHEME 9



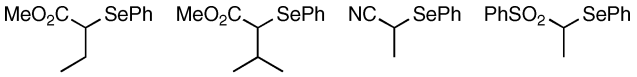
the product was subjected to stannane reduction, are known,[34] and more recently selenoxide fragmentation has been used in tandem with such condensations[35] to prepare MBH alcohols formally derived from methyl acrylate. We are aware of three additional examples[36,37] resembling the route to MBH alcohols that is summarized in Scheme 2; the more complex of these are of the type **52** → **54** → **55** (R, R′ variable), from studies toward the synthesis of a natural product (Scheme 8).[36] The other example is the single case summarized in Scheme 9.[37]

A number of attempts have been made to overcome the low reaction rate of many MBH condensations,[6] and during the present work we tried one that seemed well-suited to our needs: we treated aldehyde **12** with the aluminate **59**,[38] but did not obtain the desired adducts **13a**,**b**, recovering only starting material, even though, in a test experiment, **59** reacted smoothly (70%) with PhCHO.



59

The four selenides **60**,[39] **61**,[40] **62**,[41] and **63**[42] were prepared by conventional means: the two esters by displacement (PhSeNa) from the corresponding α-bromoesters, the nitrile by alkylation (MeI) of $PhSeCH_2CN$, and the sulfone by phenylselenation (PhSeCl) of $PhSO_2CH_2CH_3$.



60 **61** **62** **63**

Each of the selenides **60**−**63** was deprotonated with LDA in THF at −78 °C and then allowed to react with the aldehydes indicated in Table 3. The desired hydroxy selenides (see Table 3) were obtained in yields of 73−90% as isomer mixtures, and oxidation with H_2O_2 then caused elimination away from the hydroxyl-bearing carbon to give the desired alcohols, which were then acetylated, again using AcCl. With the exception of **66**, two acetates were obtained in each case, differing in stereochemistry at the acetoxy-bearing carbon. In the case of **66** there is the additional complication of *Z*/*E* isomerization, and ^{1}H NMR signals of the crude product at δ 6.92 and δ 6.22 suggest that both double bond geometries were indeed formed.

The acetates were then treated with CF_3CO_2H to remove the Boc group (Table 4). In the case of **69a** and **69b**, deprotection was slow, and a 12-h reaction period was used; in the other examples deprotection was complete within 1 h. The resulting products—presumably CF_3CO_2H salts—were dissolved in MeCN, and the solution was stirred with saturated aqueous Na_2CO_3 to afford the bicyclic amines shown in Table 4. Ring closure is easy, and even the fully substituted olefins **69a** and **69b** afforded cyclized products. The mixture of isomeric trisubstituted olefins **66** gave two isomeric amines **79a**,**b**. These must differ in stereochemistry at the methyl-bearing carbon [C(6)], but extensive NOE measurements did not allow us to establish the conformations.

Synthesis of (−)-δ-Coniceine. The sulfone **83** derived, as described above, from L-proline, was hydrogenated over Pd−C. The hydrogenation step was not facially selective, and the intermediate sulfone was obtained as a mixture of isomers, epimeric at C(6). This outcome is inconsequential, as the $PhSO_2$ group was then removed by treatment with W-2 Raney nickel, affording (−)-δ-coniceine (**85**) (Scheme 10). Attempts to use Na(Hg) for desulfonylation led to extensive ring opening, presumably via an intermediate carbanion.

(34) See: (a) Hart, D. J.; Krishnamurthy, R. *J. Org. Chem.* **1992**, *57*, 4457−4470. (b) Guindon, Y.; Faucher, A.-M.; Bourque, E.; Caron, V.; Jung, G.; Landry, S. R. *J. Org. Chem.* **1997**, *62*, 9276−9283.

(35) (a) Sheng, S.-R.; Wang, Q.; Wang, Q.-Y.; Guo, L.; Hunag, X. *Synlett* **2006**, 1887−1890. (b) Shiina, I.; Yamai, Y.; Shimazaki, T. *J. Org. Chem.* **2005**, *70*, 8103−8106.

(36) (a) Cases, M.; de Turiso, F. G.-L.; Hadjisoteriou, M. S.; Pattenden, G. *Org. Biomol. Chem.* **2005**, *3*, 2786−2804. (b) Cases, M.; de Turiso, F. G.-L.; Pattenden, G. *Synlett* **2001**, 1869−1872.

(37) Sakakibara, T.; Ikuta, S.; Sudoh, R. *Synthesis* **1982**, 261−263.

(38) (a) Ramachandran, P. V.; Reddy, M. V. R.; Rudd, M. T. *Chem. Commun.* **1999**, 1979−1980. (b) Ramachandran, P. V.; Rudd, M. T.; Burghardt, T. E.; Reddy, M. V. R. *J. Org. Chem.* **2003**, *68*, 9310−9316. (c) Tsuda, T.; Yoshida, T.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 1037−1040.

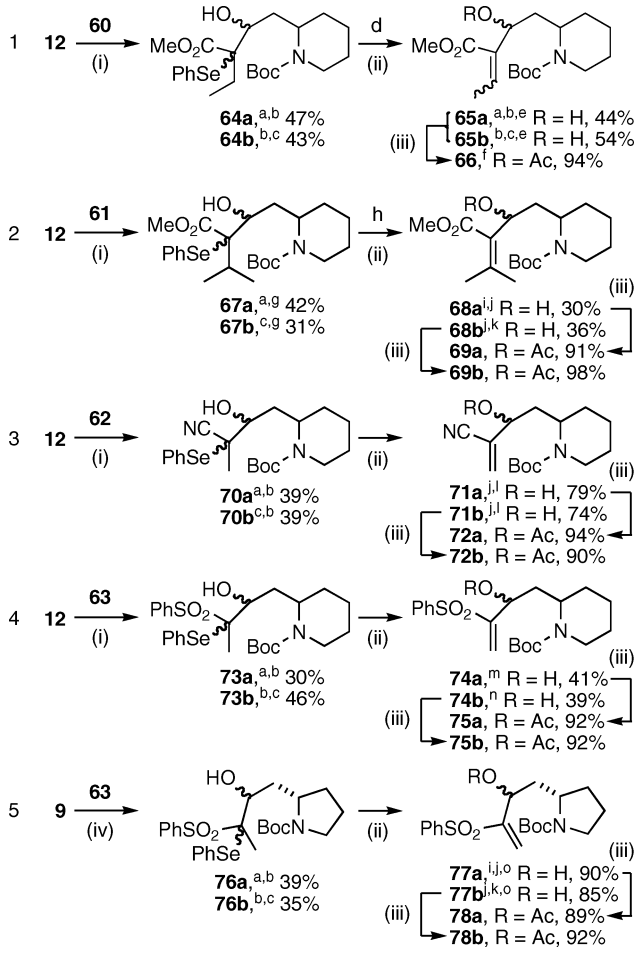
(39) Corresponding ethyl ester: Lebarillier, L.; Outurquin, F.; Paulmier, C. *Tetrahedron* **2000**, *56*, 7483−7493.

(40) Cf.: Holmes, A. B.; Nadin, A.; O'Hanlon, P. J.; Pearson, N. D. *Tetrahedron*: *Asymmetry* **1992**, *3*, 1289−1302.

(41) (a) Masuyama, Y.; Ueno, Y.; Okawara, M. *Chem. Lett.* **1977**, 835−838. (b) Arrica, M. A.; Wirth, T. *Eur. J. Org. Chem.* **2005**, 395−403.

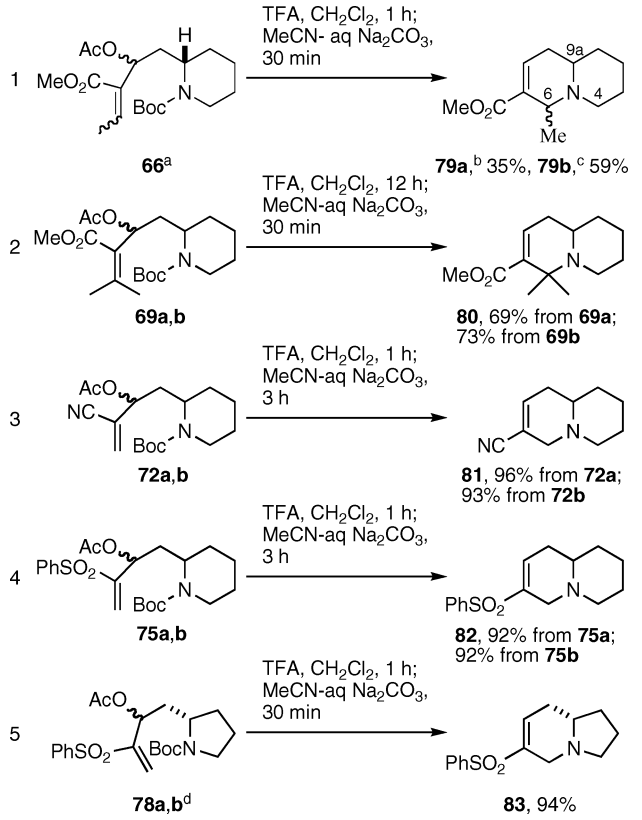
(42) Cf.: (a) Simpkins, N. S. *Tetrahedron* **1991**, *47*, 323−332. (b) Simpkins, N. S. *Tetrahedron Lett.* **1988**, *29*, 6787−6790.

TABLE 3. Selenium Route to Morita–Baylis–Hillman Adducts[p]



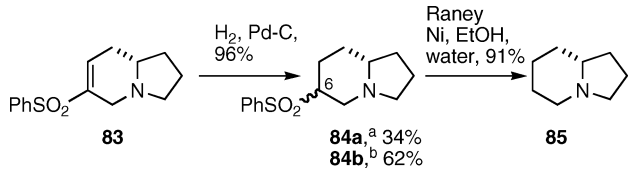
[a] More polar fraction. [b] We did not establish if the material was a mixture of isomers or a mixture of rotamers of a single isomer. [c] Less polar fraction. [d] A mixture of both fractions **64a** and **64b** was used. [e] Both **65a** and **65b** have a single double bond geometry. [f] A mixture of isomers obtained from a mixture of **65a** and **65b**. [g] Neither fraction was characterized. [h] A mixture of **67a** and **67b** was used. [i] More polar alcohol. [j] Single isomer. [k] Less polar alcohol. [l] Alcohol **71a** is derived from **70a**, while **71b** is derived from **70b**. [m] Alcohol **74a** is derived from mixture of **73a** and **73b** and is a single isomer. [n] Alcohol **74b** is derived from mixture of **73a** and **73b** and is a single isomer. [o] Alcohol **77a** is derived from **76a**, while **77b** is derived from **76b**. [p] Reagenst and conditions: (i) the indicated selenide (**60**, **61**, **62** or **63**) was deprotonated with LDA, and then aldehyde **12** was added; (ii) H_2O_2; (iii) AcCl, pyridine, CH_2Cl_2; (iv) the indicated selenide was deprotonated with LDA and then aldehyde **9** was added.

TABLE 4. Intramolecular Conjugate Displacements



[a] Isomer mixture was used. [b] More polar product. [c] Less polar product. [d] Mixture of **78a** and **78b** was used.

SCHEME 10



[a] More polar isomer. [b] Less polar isomer.

In our early experiments on this method of making bicyclic amines, we had shown that the MBH route to **10a** and **10b** proceeds with preservation of enantiomeric purity; but in making (−)-*δ*-coniceine, we did not check the enantiomeric purity of **83**, or its precursors, because the route would not be expected to compromise the ee. Our sample of the alkaloid had $[\alpha]^{20}_D$ −18.27 (*c* 0.151, EtOH) and $[\alpha]^{20}_D$ −12.50 (*c* 1.00, 95% EtOH); reported values[43]cover the range −4 to −20.

Conclusions

The method of Scheme 1 represents a general way of making bicyclic amines with nitrogen at a ring-fusion position. The method has been shown to work for a range of ring sizes and the stereochemistry α to the nitrogen is preserved in the MBH step (as judged by a test with compound **9**). The required alcohols can be prepared by the classical MBH reaction and also by the general method of Scheme 2, especially in cases where the conventional MBH reaction is very slow. The key ring closure (**5** → **6**) is independent of the degree of substitution of the double bond, and works, except where the closure would

(43) Reported values: (a) Yoda, H.; Katoh, H.; Ujihara, Y.; Takabe, K. *Tetrahedron Lett.* **2001**, *42*, 2509−2512: $[\alpha]^{23.5}_D$ −4.02 (*c* 2.12, EtOH). (b) Costa, A.; Nájera, C.; Sansano, J. M. *Tetrahedron*: *Asymmetry* **2001**, *12*, 2205−2211: $[\alpha]^{25}_D$ −10.1 (*c* 1.88, EtOH). (c) Andrés, J. M.; Herráiz-Sierra, I.; Pedrosa, R.; Pérez-Encabo, A. *Eur. J. Org. Chem.* **2000**, 1719−1726: $[\alpha]^{23}_D$ −10.1 (*c* 1.8, EtOH). (d) Sibi, M. P.; Christensen, J. W. *Tetrahedron Lett.* **1990**, *31*, 5689−5692: $[\alpha]^{27}_D$ −10.8 (*c* 1.76, EtOH). (e) Sibi, M. P.; Christensen, J. W. *J. Org. Chem.* **1999**, *64*, 6434−6442: $[\alpha]^{26}_D$ −10.8 (*c* 1.76, EtOH). (f) Waldmann, H.; Braun, M. *J. Org. Chem.* **1992**, *57*, 4444−4451: $[\alpha]^{23}_D$ −7.9 (*c* 0.15, EtOH). (g) Waldmann, H.; Braun, M.; Dräger, M. *Angew. Chem., Int. Ed.* **1990**, *29*, 1468−1471: $[\alpha]^{22}_D$ −7.9 (*c* 0.15, EtOH). (h) Ringdahl, B.; Pinder, A. R.; Pereira, W. E., Jr.; Oppenheimer, N. J.; Craig, J. C. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1−4: $[\alpha]^{23}_D$ −10.2 (*c* 1.76, EtOH). (i) Arisawa, M.; Takezawa, E.; Nishida, A.; Mori, M.; Nakagawa, M. *Synlett* **1997**, 1179−1180: $[\alpha]^{25}_D$ −20.5 (*c* 0.98, EtOH). (j) Arisawa, M.; Takahashi, M.; Takezawa, E.; Yamaguchi, T.; Torisawa, Y.; Nishida, A.; Nakagawa, M. *Chem. Pharm. Bull.* **2000**, *48*, 1593−1596: $[\alpha]^{25}_D$ −20.5 (*c* 0.98, EtOH).

be of the 5-*endo* trigonal type. The method can be used to make optically active piperidines (e.g., **39c**), and has been used to make a simple alkaloid [(−)-*δ*-coniceine]. The method has also been tested in a far more complex case relevant to the synthesis of halichlorine.[1] The products of the ring closure bear functionality—the electron-withdrawing group and the conjugated double bond—that provide opportunities for further elaboration.

Experimental Section

(2*S*)-1-(*tert*-Butoxycarbonyl)-*β*-hydroxy-α-methylene-2-pyrrolidinebutanoic Acid Methyl Ester (10a,b). DABCO (2.05 g, 18.3 mmol) and methyl acrylate (2.19 mL, 24.4 mmol) were added to aldehyde **9**[8−11](1.3 g, 6.1 mmol), and the mixture was stirred at room temperature for 3 days. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 × 20 cm), using 1:3 EtOAc−hexane, gave the less polar isomer **10b** (0.62 g, 34%) and the more polar isomer **10a** (0.71 g, 39%) as colorless oils.

More polar isomer **10a**: FTIR (CH_2Cl_2 cast) 3418, 1717, 1693, 1668 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.40 (s, 9 H), 1.64−2.01 (m, 6 H), 3.26 (t, J = 5.4 Hz, 2 H), 3.70 (s, 3 H), 3.95−4.02 (m, 1 H), 4.47 (br s, 1 H), 5.92 (br s, 1 H), 6.17 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7 (t), 28.5 (q), 32.0 (t), 43.3 (t), 46.3 (t), 51.7 (q), 55.5 (d), 69.2 (d), 79.6 (s), 124.4 (s), 143.0 (t), 155.3 (s), 166.7 (s); HRMS (ES) exact mass *m*/*z* calcd for $C_{15}H_{25}NNaO_5$ (M + Na) 322.16249, found 322.16265.

Less polar isomer **10b**: FTIR (CH_2Cl_2 cast) 3400, 1720, 1693, 1668 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.33−1.43 (m including singlet at δ 1.43, 10 H in all), 1.54 (br s, 1 H), 1.80−2.00 (m, 4 H), 3.32−3.34 (m, 2 H), 3.71 (s, 3 H), 4.16 (br s, 1 H), 4.43 (d, J = 10.3 Hz, 1 H), 5.42 (br s, 1 H), 6.00 (s, 1 H), 6.22 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.5 (t), 28.4 (q), 31.2 (t), 43.0 (t), 46.4 (t), 51.6 (q), 53.8 (d), 66.4 (d), 80.0 (s), 124.3 (s), 142.7 (t), 156.7 (s), 166.7 (s); HRMS (ES) exact mass *m*/*z* calcd for $C_{15}H_{25}NNaO_5$ (M + Na) 322.16249, found 322.16263.

(2*S*)-*β*-(Acetoxy)-1-(*tert*-butoxycarbonyl)-α-methylene-2-pyrrolidinebutanoic Acid Methyl Ester (11a,b). Pyridine (0.281 mL, 3.48 mmol) and AcCl (0.247 mL, 3.48 mmol) were added successively dropwise to a stirred and cooled (0 °C) solution of the less polar alcohol **10b** (520 mg, 1.74 mmol) in CH_2Cl_2 (15 mL). Stirring was continued for 2 h, the ice bath was removed, and stirring was continued for 1 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 × 18 cm), using 1:3 EtOAc−hexane, gave acetate **11b** (501 mg, 85%) as a colorless oil.

Under similar conditions, the more polar alcohol **10a** (500 mg, 1.67 mmol) gave the corresponding acetate **11a** (507 mg, 89%) as a colorless oil.

Acetate **11a** from the more polar alcohol: FTIR (CH_2Cl_2 cast) 1746, 1719, 1693 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38 (s, 9 H), 1.53−1.60 (m, 1 H), 1.73−1.93 (m, 4 H), 1.95−2.19 (m including singlet at δ 2.03, 4 H in all), 3.21−3.32 (m, 2 H), 3.52−3.78 (m including singlet at δ 3.70, 4 H in all), 5.53 (d, J = 10.0 Hz, 1 H), 5.72 (s, 1 H), 6.19 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0 (q), 23.0 (t), 28.5 (q), 29.8 (t), 46.2 (t), 51.9 (q), 54.3 (d), 69.6 (d), 79.0 (s), 124.4 (s), 140.1 (t), 154.2 (s), 165.5 (s), 169.9 (s); HRMS (ES) exact mass *m*/*z* calcd for $C_{17}H_{27}NNaO_6$ (M + Na) 364.17306, found 364.17329.

Acetate **11b** from the less polar alcohol: FTIR (CH_2Cl_2 cast) 1745, 1693 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.42 (s, 9 H), 1.72−1.95 (m, 5 H), 2.02 (s, 3 H), 2.07−2.15 (m, 1 H), 3.21−3.26 (m, 1 H), 3.32 (br s, 1 H), 3.70−3.81 (m including singlet at δ 3.74, 4 H in all), 5.58 (t, J = 6.6 Hz, 1 H), 5.87 (br s, 1 H), 6.29 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1 (q), 23.4 (t), 28.5 (q), 31.2 (t), 46.3 (t), 52.0 (q), 54.6 (d), 70.0 (d), 79.2 (s), 126.0 (s), 139.9 (t), 154.4 (s), 165.7 (s), 169.8 (s); HRMS (ES) exact mass *m*/*z* calcd for $C_{17}H_{27}NNaO_6$ (M + Na) 364.17306, found 364.17318.

(8a*S*)-1,2,3,5,8,8a-Hexahydro-6-indolizinecarboxylic Acid Methyl Ester (11c). CF_3CO_2H (0.226 mL, 2.93 mmol) was added to a stirred and cooled (0 °C) solution of esters **11a**,**b** (mixture of esters from the less polar and more polar alcohols) (100.0 mg, 0.293 mmol) in CH_2Cl_2 (3 mL). The ice bath was removed and stirring was continued for 1 h. The solvent was evaporated and the residue was dissolved in MeCN (3 mL). Aqueous Na_2CO_3 (20% w/v, 1 mL) was added and the mixture was stirred for 30 min. The aqueous phase was extracted with EtOAc (3 × 3 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using EtOAc, gave amine **11c** (38.0 mg, 72%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1716, 1650 cm^{-1}; $[\alpha]^{22}_D$ +195.9 (*c* 1.1, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.38−1.47 (m, 1 H), 1.70−1.92 (m, 2 H), 1.95−2.03 (m, 1 H), 2.06−2.15 (m, 2 H), 2.19 (AB q, $\Delta\nu_{AB}$ = 18.0 Hz, J = 9.2 Hz, 1 H), 2.38−2.47 (m, 1 H), 2.82−2.87 (m, 1 H), 3.21 (dt, J = 2.4, 8.8 Hz, 1 H), 3.71 (s, 3 H), 3.78−3.83 (m, 1 H), 6.97−7.00 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4 (t), 30.4 (t), 32.8 (t), 51.5 (t), 51.6 (q), 54.1 (t), 58.7 (d), 129.4 (s), 138.3 (d), 166.3 (s); HRMS (ES) exact mass *m*/*z* calcd for $C_{10}H_{15}NO_2$ 181.11028, found 181.11019. HPLC analysis [Chiracel OD−H, 5 μm, 4.6 × 250 mm, 1% EtOH−hexane, flow = 0.8 mL/min] showed the material to have an enantiomeric purity of 99.8%.

1,6,7,8,9,10,11,11a-Octahydro-4*H*-pyrido[1,2-*a*]azocine-3-carboxylic Acid Methyl Ester (26c). CF_3CO_2H (306 mg, 2.66 mmol) was added to a stirred and cooled (0 °C) solution of acetate **26a** (derived from the more polar alcohol) (102 mg, 0.266 mmol) in CH_2Cl_2 (3 mL). The cooling bath was removed and stirring was continued for 1 h. The solvent was evaporated and the residue was dissolved in MeCN (3 mL). Aqueous Na_2CO_3(20% w/v, 1 mL) was added and the mixture was stirred for 30 min. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using EtOAc, gave amine **26c** (50 mg, 84%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1715, 1664 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32−1.84 (m, 10 H), 1.96−2.30 (m, 2 H), 2.61−2.80 (m, 2 H), 2.80−2.96 (m, 1 H), 3.32 (d, J = 17.0 Hz, 1 H), 3.49 (d, J = 17.0 Hz, 1 H), 3.70 (s, 3 H), 6.94−6.98 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 26.0 (t), 26.2 (t), 26.6 (t), 27.6 (t), 31.1 (t), 33.1 (t), 50.0 (t), 51.4 (d), 52.3 (t), 56.2 (q), 129.5 (s), 138.6 (d), 166.5 (s); exact mass *m*/*z* calcd for $C_{13}H_{21}NO_2$ 223.15723, found 223.15691.

Under similar conditions, acetate **26b** (derived from the less polar alcohol) (51 mg, 0.13, mmol) gave amine **26c** (27 mg, 93%) as a colorless oil.

1,2,3,4,6,9,10,10a-Octahydropyrido[1,2-*a*]azepine-7-carboxylic Acid Methyl Ester (29c). CF_3CO_2H (237 mg, 2.06 mmol) was added to a stirred and cooled (0 °C) solution of acetate **29** (76 mg, 0.206 mmol) in CH_2Cl_2 (5 mL). The cooling bath was removed and stirring was continued for 1 h. The solvent was evaporated and the residue was dissolved in MeCN (3 mL). Aqueous Na_2CO_3 (20% w/v, 1 mL) was added and the mixture was stirred for 30 min. The aqueous phase was extracted with EtOAc (3 × 3 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using EtOAc, gave amine **29c** (41 mg, 95%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1709, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20−1.38 (m, 1 H), 1.38−1.75 (m, 6 H), 1.75−1.89 (m, 1 H), 2.17−2.58 (m, 4 H), 2.89 (d, J = 11.3 Hz, 1 H), 3.28 (d, J = 16.2 Hz, 1 H), 3.65 (s, 1 H), 3.70 (s, 3 H), 7.11−7.23 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.7 (t), 23.8 (t), 25.8 (t), 32.1 (t), 32.6 (t), 51.7 (q), 54.4 (t), 56.6 (t), 64.9 (d), 128.3 (s), 145.8 (d), 167.4 (s); exact mass *m*/*z* calcd for $C_{12}H_{19}NO_2$ 209.14159, found 209.14172.

1,3,4,6,9,10,11,11a-Octahydro-2*H*-pyrido[1,2-*a*]azocine-7-carboxylic Acid Methyl Ester (33c). CF_3CO_2H (253 mg, 2.20 mmol) was added to a stirred and cooled (0 °C) solution of acetate **33** (85

mg, 0.22 mmol) in CH_2Cl_2 (5 mL). The ice bath was removed and stirring was continued for 1 h. The solvent was evaporated and the residue was dissolved in MeCN (3 mL). Aqueous Na_2CO_3 (20% w/v, 1 mL) was added and the mixture was stirred for 30 min. The aqueous phase was extracted with EtOAc (3 × 3 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 20 cm), using EtOAc, gave amine **33c** (45 mg, 92%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1710, 1264 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.08−1.32 (m, 1 H), 1.32−1.78 (m, 8 H), 1.78−1.97 (m, 1 H), 2.02−2.40 (m, 3 H), 2.68 (br s, 1 H), 2.95 (d, J = 11.4, Hz, 1 H), 3.50−4.01 (m, 5 H), 7.21 (t, J = 8.4, Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.1 (t), 24.1 (t), 25.3 (t), 25.8 (t), 27.5 (t), 33.7 (t), 51.9 (q), 55.4 (t), 57.2 (t), 61.7 (d), 129.1 (s), 144.1 (d), 168.1 (s); exact mass m/z calcd for $C_{13}H_{21}NO_2$ 223.15723, found 223.15707.

8a-Methyl-1,2,3,5,8,8a-hexahydroindolizine-6-carboxylic Acid Methyl Ester (45c). CF_3CO_2H (0.33 mL, 4.23 mmol) was added to a stirred and cooled (0 °C) solution of acetates **45a**,**b** (mixture of both acetates) (150 mg, 0.42 mmol) in CH_2Cl_2 (5 mL). The cooling bath was removed and stirring was continued for 2 h. The solvent was evaporated and the residue was dissolved in MeCN (3 mL). Aqueous Na_2CO_3 (20% w/v, 1 mL) was added and the mixture was stirred for 30 min. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 20 cm), using EtOAc, gave amine **45c** (79 mg, 96%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1716, 1258 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.86 (s, 3 H), 1.54−1.62 (m, 1 H), 1.64−1.73 (m, 1 H), 1.74−1.82 (m, 2 H), 2.04−2.12 (m, 1 H), 2.17−2.26 (m, 1 H), 2.61−2.69 (m, 1 H), 2.83−2.91 (m, 1 H), 3.17−3.25 (m, 1 H), 3.52−3.60 (m, 1 H), 3.69 (s, 3 H), 6.94 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.3 (q), 19.9 (t), 35.7 (t), 38.4 (t), 45.0 (t), 50.0 (t), 51.4 (q), 56.4 (s), 127.6 (s), 137.7 (d), 166.5 (s); exact mass m/z calcd for $C_{11}H_{17}NO_2$ 195.12593, found 195.12554.

2-[2-Hydroxy-3-methoxycarbonyl-3-(phenylseleno)pentyl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (64a,b). BuLi (2.5 M in hexane, 0.28 mL, 0.7 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of *i*-Pr_2NH (0.13 mL, 0.9 mmol) in THF (10 mL). The solution was stirred at −78 °C for 20 min and a solution of ester **60**[39](116 mg, 0.45 mol) in THF (1 mL) was added dropwise. The mixture was stirred at −78 °C for 20 min, and then a solution of aldehyde **12**[14](93 mg, 0.412 mmol) in THF (1 mL) was added dropwise. The mixture was stirred at −78 °C for 1 h, quenched with saturated aqueous NH_4Cl (10 mL), and extracted with Et_2O (15 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm), using 8:1 hexane−EtOAc, gave the less polar phenylseleno alcohol fraction **64b** (86 mg, 43%) and the more polar phenylseleno alcohol fraction **64a** (73 mg, 47%) as colorless oils; both were used without full characterization and we did not establish if each fraction was a single isomer or a mixture of isomers.

2-[2-Hydroxy-3-(methoxycarbonyl)pent-3-enyl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (65a,b). H_2O_2 (30%, 0.15 mL) was added to a stirred solution of phenylseleno alcohols **64a**,**b** (a mixture of the less polar and more polar phenylseleno alcohol fractions) (86 mg, 0.18 mmol) in a mixture of THF (5 mL) and water (1 mL). Stirring was continued for 2 h and then water (10 mL) and Et_2O (20 mL) were added. The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 5:1 hexane−EtOAc, gave a less polar alcohol fraction **65b** (32 mg, 54%) and a more polar alcohol fraction **65a** (26 mg, 44%), both as colorless oils. Each fraction was composed of material having a single double bond geometry. The vinyl H signal of the less polar fraction had δ 6.43 and the signal for the more polar fraction had δ 6.89, suggesting that the former has a *Z* double bond and the later an *E* double bond. Both fractions were used without full characterization.

2-[2-Hydroxy-3-(methoxycarbonyl)-4-methyl-3-(phenylseleno-)pentyl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (67a,b). BuLi (2.5 M in hexane, 0.15 mL, 0.37 mmol) was added to a stirred and cooled (−78 °C) solution of *i*-Pr_2NH (40.5 mg, 0.40 mmol) in THF (10 mL). Stirring was continued for 20 min and a solution of phenylseleno ester **61**[40](101 mg, 0.37 mmol) in THF (1 mL) was then added dropwise. Stirring at −78 °C was continued for 20 min, and a solution of aldehyde **12**[14] (79 mg, 0.35 mmol) in THF (1 mL) was added dropwise. Stirring at −78 °C was continued for 1 h and the mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with Et_2O (10 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 20 cm), using 8:1 hexane−EtOAc, gave a less polar phenylseleno alcohol fraction **67b** (54 mg, 31%) and a more polar phenylseleno alcohol fraction **67a** (73 mg, 42%) as colorless oils. The individual fractions had broad ^1H NMR spectra, and were not characterized.

2-[(3-Benzenesulfonyl)-2-hydroxy-3-(phenylseleno)butyl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (73a,b). BuLi (2.5 M in hexane, 0.08 mL, 0.21 mmol) was added to a stirred and cooled (−78 °C) solution of *i*-Pr_2NH (23.3 mg, 0.23 mmol) in THF (3 mL). The cold bath was replaced by a bath at −20 °C, stirring was continued for 10 min, and then the cold bath at −78 °C was replaced. Phenylseleno sulfone **63**[42] (93 mg, 0.29 mmol) in THF (2 mL) was added dropwise and stirring was continued for 30 min. Aldehyde **12**[14] (47.7 mg, 0.21 mmol) in THF (1 mL) was added dropwise and stirring was continued for 10 min. The mixture was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with Et_2O (10 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 3:1 hexane−EtOAc, gave a more polar phenylseleno alcohol fraction **73a** (41 mg, 30%) and a less polar phenylseleno alcohol fraction **73b** (63 mg, 46%). We did not establish if each fraction was a single isomer or a mixture of isomers; the material was used without characterization.

2-[3-(Benzenesulfonyl)-2-hydroxybut-3-enyl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (74a,b). H_2O_2 (30%, 0.20 mL) was added to a stirred and cooled (0 °C) solution of phenylseleno alcohols **73a,b** (mixture of more polar and less polar fractions) (110 mg, 0.20 mmol) in THF (3 mL). Stirring was continued for 2 h and then water (5 mL) and Et_2O (10 mL) were added. The ether phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 10 cm), using 3:1 hexane−EtOAc, gave the less polar alcohol **74b** (31 mg, 39%) and the more polar alcohol **74a** (32 mg, 41%) as colorless oils.

More polar alcohol **74a**: FTIR (CH_2Cl_2 cast) 3401, 1686, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.34−1.48 (m, 11 H), 1.48−1.63 (m, 4 H), 1.71−1.85 (m, 1 H), 1.92−2.09 (m, 1 H), 2.75 (t, J = 12.1 Hz, 1 H), 3.24−3.68 (br s, 1 H), 3.86 (d, J = 13.3 Hz, 1 H), 4.24 (d, J = 4.4 Hz, 1 H), 4.36 (dd, J = 8.9, 2.6 Hz, 1 H), 6.17 (s, 1 H), 6.39 (s, 1 H), 7.49−7.65 (m, 3 H), 7.84−7.90 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.9 (t), 25.2 (t), 28.4 (q), 29.1 (t), 39.1 (t), 39.9 (t), 48.5 (d), 68.0 (d), 80.1 (s), 125.1 (s), 128.0 (d), 129.2 (d), 133.6 (d), 139.6 (s), 153.2 (t), 155.8 (s); exact mass m/z calcd for $C_{20}H_{29}NO_5S$ 395.17664, found 395.176674.

Less polar alcohol **74b**: FTIR (CH_2Cl_2 cast) 3386, 1717, 1683 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.18−1.53 (m, 13 H), 1.54−1.76 (m, 3 H), 2.43 (t, J = 14.4 Hz, 1 H), 2.96 (t, J = 12.0 Hz, 1 H), 3.92 (d, J = 13.1 Hz, 1 H), 4.01 (d, J = 10.6 Hz, 1 H), 4.40 (m, 1 H), 6.24 (s, 1 H), 6.47 (d, J = 0.9 Hz, 1 H), 7.44−7.69 (m, 3 H), 7.74−7.88 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.3 (t), 25.5 (t), 28.6 (q), 29.2 (t), 38.4 (t), 45.0 (t), 46.6 (d), 65.2 (d), 80.6 (s), 125.2 (s), 128.0 (d), 129.3 (d), 133.7 (d), 139.9 (s), 152.9 (t), 161.5 (s); exact mass m/z calcd for $C_{20}H_{29}NO_5S$ 395.17664, found 395.17540.

(2*S*)-2-[3-(Benzenesulfonyl)-2-hydroxy-3-(phenylseleno)butyl]-pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (76a,b). BuLi (2.5 M in hexane, 0.31 mL, 0.79 mmol) was added dropwise to a stirred and cooled (−78 °C) solution of *i*-Pr_2NH (0.11 mL, 0.79 mmol) in

THF (10 mL). The solution was stirred at −78 °C for 20 min and a solution of phenylseleno sulfone **63**[42] (258 mg, 0.79 mmol) in THF (5 mL) was added dropwise. The mixture was stirred at −78 °C for 1 h, and then a solution of aldehyde **9**[8] (168 mg, 0.79 mmol) in THF (5 mL) was added dropwise. The mixture was stirred at −78 °C for 1 h, quenched with saturated aqueous NH_4Cl (10 mL), and extracted with Et_2O (20 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm), using 2:1 hexane−EtOAc, gave a less polar phenylseleno alcohol fraction **76b** (149 mg, 35%) and a more polar phenylseleno alcohol fraction **76a** (166 mg, 39%) as colorless oils. We did not establish if each fraction is a mixture of isomers or a mixture of rotamers of a single isomer. Each fraction was used without characterization.

(2*S*)-2-[3-(Benzenesulfonyl)-2-hydroxybut-3-enyl]pyrrolidine-1-carboxylic Acid *tert*-Butyl Ester (77a,b). Water (1 mL), $NaHCO_3$ (34 mg, 0.40 mmol), and $NaIO_4$ (171 mg, 0.80 mmol) were added to a stirred solution of the less polar phenylseleno alcohol fraction **76b** (188 mg, 0.35 mmol) in MeOH (5 mL), and stirring was continued for 24 h. The mixture was poured into 3:17 Et_2O−pentane (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). The organic phase was washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 × 10 cm), using 3:1 hexane−EtOAc, gave alcohol **77b** (113 mg, 85%) as a colorless oil that was a single isomer.

Under similar conditions the more polar phenylseleno alcohol fraction **76a** (107 mg, 0.20 mmol) gave alcohol **77a** (68 mg, 90%) as a colorless oil, which was a single isomer and was more polar than the isomer obtained from the other fraction.

Alcohol **77a** derived from the more polar phenylseleno alcohol: FTIR (CH_2Cl_2 cast) 3395, 1667 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9 H), 1.56−169 (m, 1 H), 1.72−2.04 (m, 5 H), 3.28 (t, J = 6.9 Hz, 2 H), 3.87−3.96 (m, 1 H), 4.34−4.41 (m, 1 H), 6.21 (s, 1 H), 6.38 (s, 1 H), 7.48−7.64 (m, 3 H), 7.83−7.90 (m, 2 H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 23.7 (t), 28.5 (q), 32.5 (t), 44.4 (t), 46.3 (t), 55.5 (d), 67.9 (d), 80.0 (s), 124.6 (s), 128.0 (d), 129.2 (d), 133.5 (d), 139.6 (t), 153.6 (s), 155.9 (s); exact mass *m*/*z* calcd for $C_{19}H_{27}NNaO_5S$ (M + Na) 404.15022, found 404.15049.

Alcohol **77b** derived from the less polar phenylseleno alcohol: FTIR (CH_2Cl_2 cast) 3366, 1665 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 9 H), 1.51−1.61 (m, 2 H), 1.77−1.98 (m, 4 H), 3.26−3.36 (m, 2 H), 4.01−4.15 (m, 1 H), 4.28 (d, J = 9.9 Hz, 1 H), 5.01−5.60 (br s, 1 H), 6.21 (s, 1 H), 6.46 (s, 1 H), 7.55−7.63 (m, 3 H), 7.82−7.89 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.4 (t), 28.3 (q), 31.1 (t), 43.5 (t), 46.5 (t), 53.5 (d), 65.3 (d), 80.1 (s), 124.7 (s), 128.2 (d), 129.0 (d), 133.3 (d), 139.6 (t), 152.9 (t), 156.7 (s); exact mass *m*/*z* calcd for $C_{19}H_{27}NNaO_5S$ (M + Na) 404.15022, found 404.15006.

6-Methyl-1,3,4,6,9,9a-hexahydro-2*H*-quinolizine-7-carboxylic Acid Methyl Ester (79a,b). CF_3CO_2H (93.2 mg, 0.81 mmol) was added to a stirred and cooled (0 °C) solution of acetates **66** (30 mg, 0.081 mmol) in CH_2Cl_2 (2 mL). The cooling bath was removed and stirring was continued for 1 h. The solvent was evaporated and residue was dissolved in MeCN (2 mL) and aqueous Na_2CO_3 (20% w/v, 0.5 mL) was added. The mixture was stirred for 30 min then extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 8 cm), using EtOAc, gave the less polar amine **79b** (10 mg, 59%) and the more polar amine **79a** (6 mg, 35%) as colorless oils.

More polar amine **79a**: FTIR (CH_2Cl_2 cast) 1715 1257 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.16 (d, J = 6.6 Hz, 2 H), 1.22−1.45 (m, 3 H), 1.48−1.92 (m, 4 H), 2.16−2.34 (m, 2 H), 2.48−2.66 (m, 1 H), 2.69−2.90 (m, 2 H), 3.68−3.84 (m, 4 H), 6.94 (t, J = 3.9, Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9 (q), 22.8 (t), 25.8 (t), 31.3 (t), 32.9 (t), 47.5 (d), 50.4 (t), 51.4 (q), 54.1 (d), 133.7 (s), 136.5 (d), 166.1 (s); exact mass *m*/*z* calcd for $C_{12}H_{19}NO_2$ 209.14159, found 209.14109.

Less polar amine **79b**: FTIR (CH_2Cl_2 cast) 1716, 1256 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.12−1.40 (m, 5 H), 1.42−1.80 (m, 4 H), 1.95 (dt, J = 2,6, 11.7 Hz, 1 H), 2.06 (d, J = 2.6 Hz, 3 H), 3.02−3.18 (m, 1 H), 3.25 (d, J = 11.9 Hz, 1 H), 3.70 (s, 3 H), 6.84−6.92 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.9 (q), 24.2 (t), 26.0 (t), 33.3 (t), 33.4 (t), 51.4 (q), 53.3 (t), 56.0 (d), 57.1 (d), 134.0 (s), 136.0 (d), 167.4 (s); exact mass *m*/*z* calcd for $C_{12}H_{19}NO_2$ 209.14159, found 209.14115.

(8a*S*)-6-(Benzenesulfonyl)-1,2,3,5,8,8a-hexahydroindolizine (83). CF_3CO_2H (0.13 mL, 1.65 mmol) was added to a stirred and cooled (0 °C) solution of acetates **78a**,**b** (mixture of more polar and less polar isomers) (70 mg, 0.17 mmol) in CH_2Cl_2 (5 mL). The ice bath was removed and stirring was continued for 2 h. The solvent was evaporated and the residue was dissolved in MeCN (3 mL). Aqueous Na_2CO_3 (20% w/v, 1 mL) was added and the mixture was stirred for 30 min. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 20 cm), using EtOAc, gave amine **83** (41 mg, 94%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2791 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.36−1.47 (m, 1 H), 1.70−1.90 (m, 2 H), 1.95−2.06 (m, 1 H), 2.09−2.23 (m, 3 H), 2.55 (ddd, J = 14.6, 5.6, 2.9 Hz, 1 H), 2.93−3.03 (m, 1 H), 3.11 (dt, J = 2.4, 8.8 Hz, 1 H), 3.55 (d, J = 15.8 Hz, 1 H), 7.06−7.11 (m, 1 H), 7.49−7.63 (m, 3 H), 7.84−7.89 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.4 (t), 30.1 (t), 32.3 (t), 50.1 (t), 53.8 (t), 58.5 (d), 127.9 (d), 129.2 (d), 133.3 (d), 137.6 (d), 139.2 (s), 139.4 (s); exact mass *m*/*z* calcd for $C_{14}H_{17}NO_2S$ 263.09799, found 263.09785.

(8a*S*)-6-(Benzenesulfonyl)octahydroindolizine (84a,b). Pd−C (10% Pd on C, 50 mg) was added to a solution of amine **83** (500 mg, 1.90 mmol) in dry EtOH (20 mL) and the mixture was hydrogenated at room temperature in a Parr shaker (initial pressure 58 psi) for 48 h. The mixture was filtered and the filtrate was evaporated. Flash chromatography of the residue over silica gel (2 × 20 cm), using 5% MeOH−CH_2Cl_2, gave the less polar saturated sulfone **84b** (312 mg, 62%) and the more polar sulfone **84a** (173 mg, 34%) as colorless oils.

More polar sulfone **84a**: FTIR (CH_2Cl_2 cast) 2790, 2730 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.48−1.60 (m, 1 H), 1.62−1.71 (m, 1 H), 1.72−1.92 (m, 5 H), 1.97−2.10 (m, 1 H), 2.67−2.80 (m, 2 H), 2.80−2.93 (m, 2 H), 3.11 (dd, J = 12.0, 7.7 Hz, 1 H), 3.40−3.49 (m, 1 H), 7.49−7.67 (m, 3 H), 7.86−7.92 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.9 (t), 20.8 (t), 24.4 (t), 27.2 (t), 47.2 (t), 53.9 (t), 59.3 (d), 60.3 (d), 128.9 (d), 129.1 (d), 133.9 (d), 138.0 (s); exact *m*/*z* calcd for $C_{14}H_{19}NO_2S$ 265.11365, found 265.11295.

Less polar sulfone **84b**: FTIR (CH_2Cl_2 cast) 2791, 2730 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.018−1.45 (m, 3 H), 1.55−1.98 (m, 5 H), 2.11−2.29 (m, 3 H), 3.03 (dt, J = 2.3, 9.0 Hz, 1 H), 3.30−3.41 (m, 2 H), 7.51−7.69 (m, 3 H), 7.82−7.89 (m, 2 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.9 (t), 23.9 (t), 28.6 (t), 29.5 (t), 50.8 (t), 53.4 (t), 60.6 (d), 63.5 (d), 128.7 (d), 129.2 (d), 133.8 (d), 137.5 (s); exact mass *m*/*z* calcd for $C_{14}H_{19}NO_2S$ 265.11365, found 265.11295.

(8a*R*)-Octahydroindolizine [(−)-δ-Coniceine] (85).[43] Sulfone **84a**,**b** (mixture of more polar and less polar sulfones) (200 mg, 0.75 mmol) in EtOH (30 mL) was refluxed with freshly activated W-2 Raney-Nickel catalyst[44]in water (2.08 g of the moist solid) under Ar. After 3 h, the mixture was filtered and the filtrate was evaporated. Flash chromatography of the residue over silica gel (1 × 25 cm), using 10:1 CH_2Cl_2−MeOH, gave δ-coniceine **85** (85 mg, 91%) as a colorless oil: $[\alpha]^{20}_D$ −18.27 (*c* 0.151, EtOH), $[\alpha]^{20}_D$ −12.50 (*c* 1.0, EtOH);[43] ^1H NMR ($CDCl_3$, 400 MHz) δ 1.07−1.24 (m, 2 H), 1.26−1.39 (m, 1 H), 1.41−1.82 (m, 8 H), 1.89 (dt, J = 3.3, 11.5 Hz, 1 H), 1.99 (q, J = 8.9 Hz, 1 H), 2.94−3.07 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.6 (t), 24.5 (t), 25.5 (t), 30.5 (t), 31.1 (t), 53.1 (t), 54.3 (t), 64.3 (d).

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Supporting Information Available: Experimental procedures for **13a**,**b**; **14a**,**b**,**c**; **18**; **19a**,**b**; **20a**,**b**,**c**; **22**; **23**; precursor to **24**; **24**; **25a**,**b**; **26a**,**b**; **28**; **29**; precursor to **31**; **32**; **33**; **35**; **36**; **36c**; **38a**,**b**; **39a**,**b**,**c**; **40**; **41**; **42**; **43**; **44a**,**b**; **45a**,**b**; **60**; **61**; **66**; **68a**,**b**; **69a**,**b**; **70a**,**b**; **71a**,**b**; **72a**,**b**; **75a**,**b**; **78a**,**b**; **80**; **81**; **82** and NMR spectra of **10a**,**b**; **11a**,**b**,**c**; **13a**,**b**; **14a**,**b**,**c**; **18**, **19a**,**b**; **20a**,**b**,**c**; **23**; precursor to **24**; **24**; **25a**,**b**; **26a**,**b**,**c**; **28**; **29**; **29c**, hydrogenation product of **30**, **32**; **33**; **33c**; **35**; **36**; **36c**; **38a**,**b**; **39a**,**b**,**c**; **41**; **43**, **44a**,**b**; **45a**,**b**,**c**; **60**; **61**; **68a**,**b**; **69a**,**b**; **70a**,**b**; **71a**,**b**; **72a**,**b**; **74a**,**b**; **75a**,**b**; **77a**,**b**; **78a**,**b**; **79a**,**b**; **80**−**83**, **84a**,**b**; **85**. This material is available free of charge via the Internet at http://pubs.acs.org.

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