Biomimetic Total Synthesis of Pseudotabersonine: A Novel Oxindole-Based Approach to Construction of *Aspidosperma* Alkaloids

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The biosynthesis of the *Aspidosperma* alkaloid pseudotabersonine **3** proceeds via the postulated dehydrosecodine **2** derived from the *Strychnos* alkaloid stemmadenine **1**.[1] The lack of biomimetic approaches to **3** has primarily been due to the inherent instability of the dihydropyridine portion of dehydrosecodine **2**. The one published account detailing a biomimetic approach to the construction of a pentacyclic *Aspidosperma* alkaloid (N^1-benzylpseudotabersonine) employs a dehydrosecodine masked as a tricarbonylchromium(0) complex.[2] We wish to report a biomimetic total synthesis of pseudotabersonine **3** which proceeds via the intermediacy of a dehydrosecodine and features a novel approach to the construction of *Aspidosperma* alkaloids.[3]

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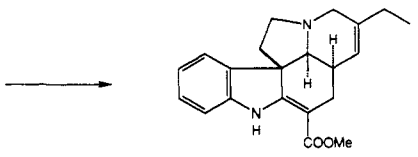

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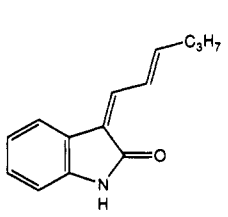
The synthesis of pseudotabersonine commences with oxindole, which is condensed with *trans*-2-hexenal in refluxing toluene–triethylamine (5:1), giving rise (65%) after 18 h to a readily separable mixture of **4** and **5** in a ratio of 1.2:1. Treatment of **4** with 2.0 equiv of potassium diisopropylamide[4] in tetrahydrofuran at −78 °C followed by the addition of 1.0 equiv of spiroaziridinium triflate **6**[5] and warming to ambient temperature (2 h) afforded the alkylated oxindole **7** (R = H) in 53% yield. Similar treatment of **5** gave rise to **7** (R = H) in comparable yield.

Prior to unraveling of the azanorbornene fragment in **7** (R = H), the oxindole nitrogen was benzylated (KO-*t*-Bu, THF, BnCl, Bu_4NI, 24 h), giving rise to **7** (R = Bn) in 65% yield. It was anticipated that subjection of **7** (R = Bn) to a tandem retro Diels–Alder/intramolecular aza Diels–Alder reaction[6] under aprotic conditions would lead to spirotetracyclic oxindole formation. Indeed exposure of a 0.02 M solution of **7** (R = Bn) in toluene with 1.2 equiv of boron trifluoride etherate at 100 °C for 2 h provided (61%) a readily separable mixture of **8** and **9** in a ratio of 1.5:1. The formation of isomeric oxindoles **8** and **9** is of no consequence, since both compounds, either as a mixture or as pure entities, have been converted into pseudotabersonine via dehydrosecodine **11** (eq 1).



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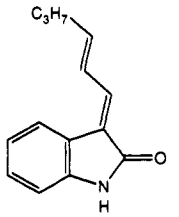

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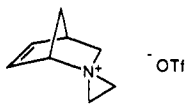

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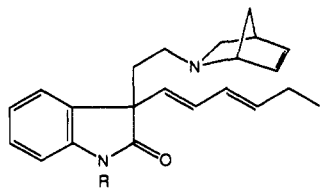

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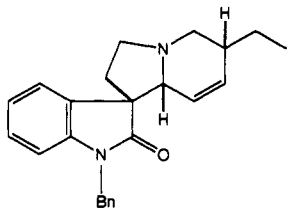

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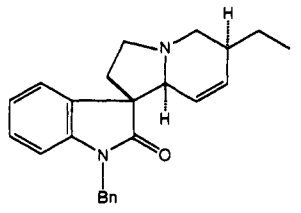

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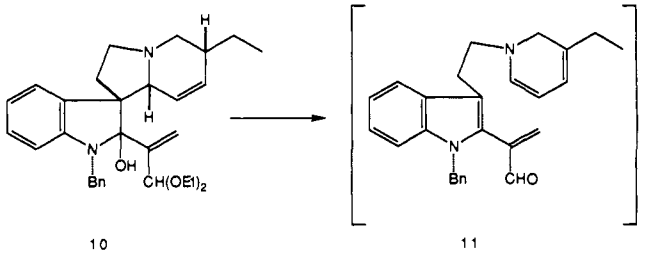
Addition of 2-lithio-1,1-diethoxy-2-propene[7] to oxindole **8** in tetrahydrofuran provided carbinolamine **10** in 95% yield, which set the stage for in situ dehydrosecodine formation and subsequent intramolecular Diels–Alder reaction (eq 1). Toward this end, a 0.02 M solution of carbinolamine **10** in acetone containing 20 equiv of water was treated with 1.1 equiv of *p*-toluenesulfonic acid at ambient temperature. After 2 h, acetonitrile was added, the temperature was raised to 80 °C, and excess triethylamine was added. Workup provided a 50% yield of **12**, possessing the intact pentacyclic carbon skeleton of pseudotabersonine.



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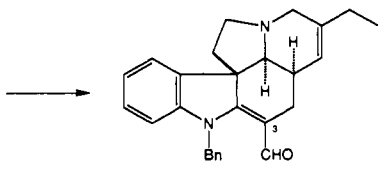

(1)

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Completion of the total synthesis necessitated transformation of the formyl group at C(3) into a carbomethoxy unit and removal of the N^1-benzyl group. All attempts to oxidize **12** met with no success. Hydrolytic deformylation[8] of **12** with 2 N hydrochloric acid at 120 °C (1.75 h) followed by treatment with neutral alumina gave rise to an 81% yield of **13**. Denbenzylation proved to be equally problematic. However, addition of **13** to 30 equiv

(1) Wenkert, E. *J. Am. Chem. Soc.* **1962**, *84*, 98. Scott, A. I. *Bioorg. Chem.* **1974**, *3*, 398. Kutney, J. P. *Heterocycles* **1977**, *7*, 593.
(2) Kutney, J. P.; Karton, Y.; Kawamura, N.; Worth, B. R. *Can. J. Chem.* **1982**, *60*, 1269.
(3) For a recent synthesis of pseudotabersonine, see: Bornmann, W. G.; Kuehne, M. E. *J. Org. Chem.* **1992**, *57*, 1752.
(4) Raucher, S. R.; Koolpe, G. A. *J. Org. Chem.* **1978**, *43*, 3794.
(5) Grieco, P. A.; Carroll, W. A. *Tetrahedron Lett.* **1992**, *33*, 4401.
(6) The trapping of immonium ions, generated in situ from retro Diels–Alder reactions of N-substituted 2-azanorbornenes, with triethylsilane/trifluoroacetic acid has been reported (Grieco, P. A.; Bahsas, A. *J. Org. Chem.* **1987**, *52*, 5746).
(7) Ficini, J.; Depezay, J.-C. *Tetrahedron Lett.* **1969**, 4797.
(8) Cf.: Weissmann, Ch.; Schmid, H.; Karrer, P. *Helv. Chim. Acta* **1961**, *44*, 1877.

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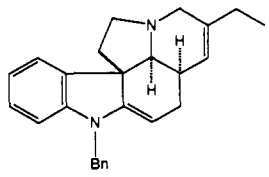

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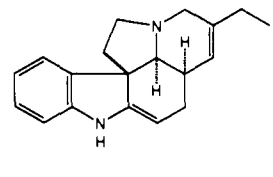

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of lithium 4,4′-di-*tert*-butylbiphenylide[9] in tetrahydrofuran at −5 °C provided after 1 h an 87% yield of **14**. Installation of the C(3) carbomethoxy group was realized in 35% yield by treatment [−78 °C (30 min) → 0 °C (15 min)] of **14** with lithium diisopropylamide in tetrahydrofuran followed by addition of excess methyl chloroformate at −78 °C and warming to ambient temperature (30 min). The spectral properties (^{1}H NMR, IR, UV, MS) of synthetic pseudotabersonine were found to be identical with those of an authentic sample of (−)-pseudotabersonine.

The synthesis of pseudotabersonine is noteworthy in that it features (1) a novel use of the spiroaziridinium salt **6**, (2) a unique tandem retro Diels–Alder/intramolecular aza Diels–Alder sequence [**7** (R = Bn) → **8** + **9**], and (3) an unprecedented oxindole-based strategy leading to the in situ generation of dehydrosecodine **11**.

Acknowledgment. This investigation was supported by a Public Health Service Research Grant from the National Institute of General Medical Sciences (GM 33605). We are grateful to Professor Martin Kuehne for providing the ^{1}H NMR spectrum of (+)-pseudotabersonine and Professor Jean Lévy for an authentic sample of (−)-pseudotabersonine.

(9) Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.* **1980**, *45*, 1924.

The β-(Phosphonooxy)alkyl Radical Rearrangement†

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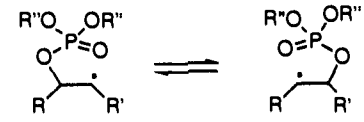
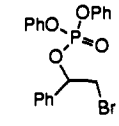
The acyloxy and allylhydroperoxy migrations originally described by Surzur[1] and Schenck,[2] respectively, have been the subjects of much investigation[3,4] over a number of years. We considered that an analogous 1,2-migration of phosphate esters (Scheme I) must exist and present here the results of our experiments which demonstrate that this is indeed the case.[5,6]

Scheme I



Reaction of styrene bromohydrin with diphenyl phosphorochloridate gave the bromo phosphate **1**. Dropwise addition of a benzene solution of tributyltin hydride (TBTH) and 10 mol % of AIBN over 25 h into a solution of **1** in benzene at reflux under nitrogen cleanly gave the reduction product (**2**) and the rearrangement product (**3**) in a ratio of 1:4.[7] Under more concentrated conditions or with more rapid addition of the stannane, greater amounts of the simple reduction product (**2**) were observed; nevertheless, even simple heating of a mixture of **1** (0.025 M) and TBTH (0.05 M) to reflux in benzene with AIBN resulted in the isolation of 23% of **3**. Mindful that **2** could also have arisen by 1,2-migration of the phenyl group, the deuterio analogue (**4**) of **1** was prepared and treated with stannane and AIBN under the optimum conditions determined for **1**, resulting in the clean formation of **5** with no trace of **6** as determined by 300-MHz ^{1}H NMR examination of the crude reaction mixture.[8] Evidently the phosphonooxy migration is significantly faster than a neophyl rearrangement. In a second example, a mixture of the bromo phosphate **7** and TBTH were heated to reflux, with AIBN initiation, in benzene leading cleanly to the rearrangement product (**8**) essentially quantitatively. The difference in rate between this example and the rearrangement of **1** to **3** was marked and probably reflects the imposed favorable orientation both of the first-formed radical and of the scissile benzylic C–O bond.



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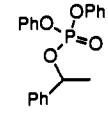

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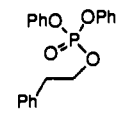

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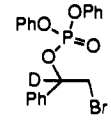

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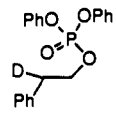

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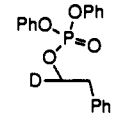

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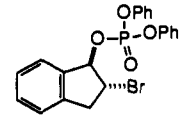

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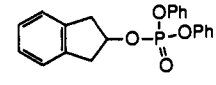

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A third example was provided by the phosphorylated bromohydrin **9** which reacted with TBTH and AIBN under the standard

† Dedicated respectfully to Professor Jean-Marie Surzur on his retirement.

(1) (a) Surzur, J.-M.; Teissier, P. *C. R. Acad. Sci. Fr., Ser. C* **1967**, *264*, 1981. (b) Surzur, J.-M.; Teissier, P. *Bull. Soc. Chim. Fr.* **1970**, 3060. (c) Also see: Tanner, D. D.; Law, F. C. P. *J. Am. Chem. Soc.* **1969**, *91*, 7537.

(2) Schenck, G. O.; Neumuller, O. A.; Eisfeld, W. *Liebigs Ann. Chem.* **1958**, *618*, 202.

(3) Acetoxy migration: (a) Beckwith, A. L. J.; Duggan, P. J. *J. Chem. Soc., Chem. Commun.* **1988**, 1000. (b) Beckwith, A. L. J.; Radom, L.; Saebo, S. *J. Am. Chem. Soc.* **1984**, *106*, 5119. (c) Barclay, L. R. C.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1984**, *106*, 1793. (d) Barclay, L. R. C.; Griller, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1982**, *104*, 4399. (e) Korth, H. G.; Sustmann, R.; Gröninger, K. S.; Leisung, M.; Giese, B. *J. Org. Chem.* **1988**, *53*, 4364. (f) Kocovsky, P.; Stary, I.; Turecek, F. *Tetrahedron Lett.* **1986**, *27*, 1513. (g) Giese, B.; Gilges, S.; Gröninger, K. S.; Lamberth, C.; Witzel, T. *Liebigs Ann. Chem.* **1988**, 615. (h) Giese, B.; Gröninger, K. S.; Witzel, T.; Korth, H.-G.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 233. (i) Giese, B.; Kopping, B. *Tetrahedron Lett.* **1989**, *30*, 681.

(4) Allylhydroperoxy migration: (a) Brill, W. F. *J. Chem. Soc., Perkin Trans. 2* **1984**, 621. (b) Brill, W. F. *J. Am. Chem. Soc.* **1965**, *87*, 3286. (c) Porter, N. A.; Wujek, J. S. *J. Org. Chem.* **1987**, *52*, 5085. (d) Porter, N. A.; Zuraw, P. *J. Chem. Soc., Chem. Commun.* **1985**, 1472. (e) Beckwith, A. L. J.; Davies, A. G.; Davison, I. G. E.; Maccoll, A.; Mruzek, M. H. *J. Chem. Soc., Perkin Trans. 2* **1989**, 815. (f) Davies, A. G.; Davison, I. G. E. *J. Chem. Soc., Perkin Trans. 2* **1989**, 825. (g) Avila, D. V.; Davies, A. G.; Davison, I. G. E. *J. Chem. Soc., Perkin Trans. 2* **1988**, 1847. (h) Mills, K. A.; Caldwell, S. E.; Dubay, G. R.; Porter, N. A. *J. Am. Chem. Soc.* **1992**, *114*, 9689.

(5) To our knowledge the closest analogy to the migrations described herein involves the photostimulated rearrangement of an α-keto phosphite to an enolphosphate: Griffin, C. E.; Bentrude, W. G.; Johnson, G. M. *Tetrahedron Lett.* **1969**, 969.

(6) A related intermolecular process in which methyl and phenyl radicals displace ethyl radicals from triethyl phosphate, when generated in the latter as solvent, has been described by Levin: (a) Levin, Ya. A.; Truteva, E. K.; Gozman, I. P.; Abul'khanov, A. G.; Ivanov, B. E. *Izv. Akad. Nauk SSSR Ser. Khim.* **1970**, 2844. (b) Levin, Ya. A.; Truteva, E. K.; Ivanov, B. E. *J. Gen. Chem. USSR* **1974**, *44*, 1418.

(7) Typical experimental procedure: To a solution of **1** (104 mg, 0.25 mmol) in C_6H_6 (40 mL) at reflux under N_2 was added a solution of TBTH (87 mg, 0.30 mmol) and AIBN (3.5 mg, 0.025 mmol) in C_6H_6 (20 mL) over 25 h with a motor-driven syringe pump. After the reaction was cooled to room temperature, the solvent was removed in vacuo and the residue examined by ^{1}H NMR spectroscopy at 300 MHz. The products **2** and **3** were identified by comparison with the spectra of authentic samples.

(8) The bromo phosphates **1**, **13**, **15** and the glycoside **9** were each recovered unchanged after 24 h at reflux in benzene, indicating that the reactions observed did not occur by an ionic rearrangement to their regioisomers followed by reduction with the stannane.

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