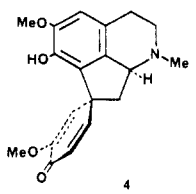
the H-7α signal at δ 2.00 and to a 4% enhancement of the H-8_{eq} multiplet at δ 1.52. It was also possible to interconnect H-8_{eq} (δ 1.52) with H-9_{eq} (δ 1.87) through an 8% NOE. Finally, since H-8_{ax} and H-9_{eq} can be interrelated to H-10_{ax} as shown in diagram **2**-NOE, it follows that the C-10 alcohol is equatorial.

The mass spectrum was in line with the structure assignment for (−)-misramine (**2**). A strong molecular ion (71%), m/z 331, is flanked by an even stronger (86%) m/z 330 peak due to loss of a hydrogen. The base peak, m/z 316, is caused by loss of a methyl from the molecular ion. Another strong peak, m/z 288 (48%), represents the fragment formed from the molecular ion by loss of CH_2-NCH_3 through a retrodiene condensation.[3]

Misramine is levorotatory, $[\alpha]^{25}_D$ −23° (*c* 0.1, MeOH), −26° (*c* 0.1, C_6H_6), −22° (*c* 0.1, acetone), indicating that it possesses the *S* configuration as in expression **2**.[1,5] Additionally, the CD curve of (−)-misramine (**2**) in methanol exhibits $\Delta\epsilon$ (nm) 0 (300), −2.6 (280), −0.6 (225), −5 (242), 0 (230). This pattern with a double minimum is typical of a proaporphine of the *S* configuration possessing a saturated ring D.[6]

The characterization of (−)-misramine (**2**) relates to an interesting facet of proaporphine chemistry. Six "normal" type proaporphine–benzylisoquinoline dimers are known which incorporate an anti relationship between H-6a and the aryloxy substituent on ring D.[7] On the other hand, only two proaporphine–benzylisoquinolines of the alternate "epi" series have been characterized in which H-6a and the ring-D aryloxy substituent lie syn to each other.[7,8] Dimers of the epi series appear to occur less frequently than their counterparts of the normal configuration, although all are known to be present solely among members of the botanical family Berberidaceae.[7,8]

Among the monomeric proaporphines, however, only one alkaloid has been completely characterized which posseses an extra oxygenated function on ring D. This is the Papaveraceae base (−)-orientalinone (**4**) which partakes of the epi configuration[7] and is known to be derived biogenetically from the tetrahydrobenzylisoquinoline (+)-orientaline (**5**).[9]



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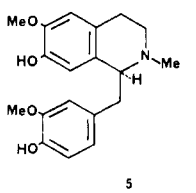

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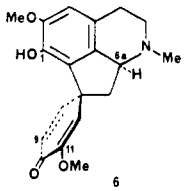

6

The results presently described indicate that enzymatic oxidation of (+)-orientaline (**5**) may lead to a normal-type monomeric proaporphine such as **6**, which through reduction and intramolecular cyclization can lead to (−)-misramine (**2**) which is also of the normal series.[10] The cyclization to form the fifth ring occurs at C-11 rather than at C-9 since, aside from electronic factors, molecular models and NMR NOEDS studies indicate that for proaporphines or dihydroproaporphines of the *S* configuration the C-1 phenol is closer to C-11 than to C-9.[7] We conclude that the botanical families Papaveraceae and Berberidaceae are both capable of producing proaporphines of the normal as well as of the epi configurations.

Acknowledgment. This research was supported by NSF Grant CHE-8210699 to M.S.

Registry No. **2**, 94801-27-1.

(4) Hall, L. D.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1980**, *102*, 5703. Geminal NOE's for the hydrogens at C-4, C-5, C-7, C-8, C-9, and C-12 have not been included in diagram 2-NOE. Geminal NOE's are usually on the order of 13%.

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(8) Weiss, I.; Freyer, A. J.; Shamma, M.; Urzúa, A. *Heterocycles* **1984**, *22*, 2231. *Normal* dimers include (+)-pakistanamine, (+)-valdiberine, (+)-berbivaldine, (+)-valdivianine, (+)-patagonine, and (+)-rupancamine. Epi dimers are (+)-epivaldiberine and (+)-epiberbivaldine.

(9) Battersby, A. R.; Brown, R. T.; Clements, J. H.; Iverach, G. C. *Chem. Commum.* **1965**, 230. Battersby, A. R.; Brocksom, T. J.; Ramage, R. *Chem. Chem.* **1969**, 464.

(10) The proaporphine (−)-rhoehybrine was also obtained from *Roemeria*. It corresponds to an 8,9,11,12-tetrahydroorientalinone derivative. Its stereochemistry has not been discussed, although it probably possesses the C-6a *S* configuration since it is levorotatory. See: Slavík, L.; Dolejš, L.; Slavíkova, L. *Collect. Czech Chem. Commun.* **1974**, *39*, 888.

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Tandem Conjugate Addition–Aldol Reactions Employing 9-(Phenylseleno)-9-borabicyclononane: A Novel Method for Effecting Formal Aldol Condensations at the α-Carbon of α,β-Unsaturated Ketones

Summary: The title compound has been shown to undergo conjugate addition to a variety of α,β-unsaturated ketones to afford β-seleno boron enolates which are convertable to unsaturated ketols upon treatment with aldehydes and subsequent oxidative elimination.

Sir: Over the last several years the general synthetic utility of bifunctional, neutral molecules which contain both hard acid and soft base components has been widely recognized.[2-8] The vast majority of reagents within this category are derived from metals or metalloids (in particular Si and Al) which exhibit a strong affinity for oxygen. In this communication we report the preparation and some of the synthetic applications of the *B*-(phenylseleno)dialkylboranes **1a,b**, members of a new class of highly reactive bifunctional reagents. The synthesis of the selenoborinate reagents **1a,b** can be conveniently accomplished by treating

(1) W.R.L. gratefully acknowledges receipt of an Allied Chemical Dissertation Fellowship.

(2) Evans, D. A.; Grimm, K. G.; Truesdale, L. K. *J. Am. Chem. Soc.* **1975**, *97*, 3229.

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(8) Kozikowski, A. P.; Ames, A. *J. Org. Chem.* **1978**, *43*, 2735.

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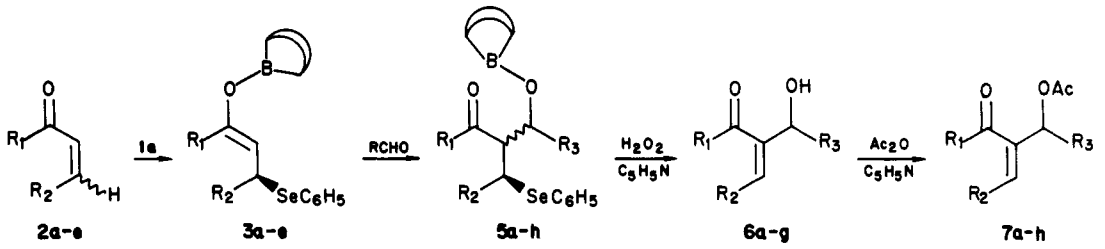
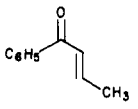
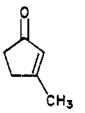
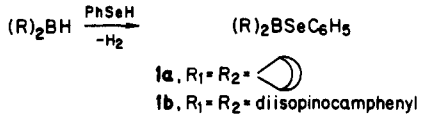
Table I



enone 2	β-phenylseleno[a] enolate 3 (%)	aldehyde	ketol 6 (%)	ketol acetate 7 (%)
 2a	100	C_6H_5CHO *i*-PrCHO	6a, 67 6b, 67	7a, 65 7b, 60
 2b	100	C_6H_5CHO *i*-PrCHO	6c, 24 6d, 71	7e,[18] 77 7d, 63
 2c	100	C_6H_5CHO *i*-PrCHO	6e, 83[b] 6f, 76[c]	7e, 74 7f, 71
 2d	100	C_6H_5CHO *i*-PrCHO	6g, 22 6h, ~0	7g, 49 7h, 57
 2e	30[d]			

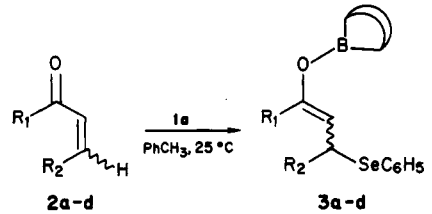
[a] The extent of enolate formation was determined by NMR spectroscopy with 1a prepared in C_6D_6. [b] *E*:*Z* product ratio = 2.2:1.[19] [c] *E*:*Z* product ratio = 2.3:1.[19] [d] In addition, 70% of the product resulting from 1,2-addition of 1a to 2e was formed.

benzeneselenol with the corresponding dialkylborane (1 equiv) in toluene (60 °C, 5 h).[9] The reagents **1a** and **1b**



are sensitive to both oxygen and moisture but can be safely stored as stock solutions in the dark for several weeks.

9-(Phenylseleno)-9-borabicyclononane (**1a**) was found to react with a variety of α,β-unsaturated ketones with varying degrees of facility. Accordingly, exposure of the enones **2a–d** to the selenoborinate **1a** ($PhCH_3$, 25 °C, 2 H) generated the boron enolates **3a–d** as the exclusive addends in quantitative yield (Table I). The rate of addition



was neither depressed by the introduction of galvinoxyl nor enhanced in the presence of the radical initiator AIBN under irradiation.[10,11] In contrast to the aforementioned observations at 25 °C, treatment of the α,β-unsaturated ketone **2a** (1.1 equiv) with the selenoborinate **1a** (1 equiv) at −78 °C generated the intermediate **4**. Upon warming to 25 °C, the 1,2-adduct was smoothly converted to the corresponding enolate **3a**.[12] The mechanistic implications suggested by these data are that 1,2-adducts are kinetically favored while the products generated by 1,4-addition are thermodynamically more stable.[13] In accordance with this rational, treatment of the α,β-unsaturated ketone **2e** with the selenoborinate **1a** ($PhCH_3$, 25 °C, 1 h) afforded a 7:3 mixture of the products resulting from 1,2- and 1,4-addition.

The synthetic utility of the β-phenylseleno enolate adducts was subsequently examined. Sequential treatment of the α,β-unsaturated ketone **2a** with the selenoborinate **1a** ($PhCH_3$, 25 °C, 2 h) followed by the addition of benz-

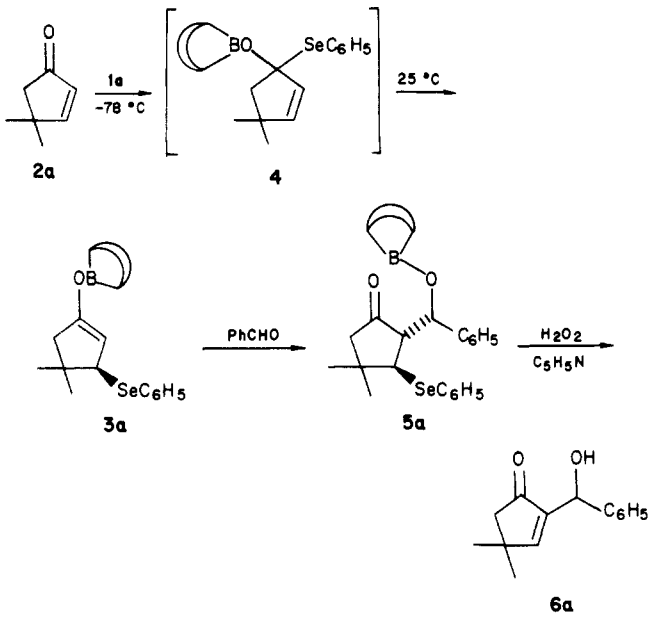
(9) A typical experimental procedure is as follows: An oven-dried 50-mL volumetric flask equipped with a magnetic stirring bar and rubber septum was charged with 3.6887 g of 9-borabicyclononane (30.23 mmol) under a nitrogen atmosphere. This was dissolved in 30 mL of dry toluene followed by the addition of 3.20 mL of benzeneselenol (30.23 mmol). The mixture was warmed to 50 °C until the cessation of hydrogen evolution (5 h). The stock solution was adjusted to 0.605 M by suspending the stirring bar in the void volume with a magnet, followed by the addition of the remaining toluene. The solution was stored at −20 °C in the dark.

(10) These results are inconsistent with a radical mechanism for the addition of **1a** to α,β-unsaturated ketones.

(11) Kabalka, G. W.; Brown, H. C.; Suzuki, A.; Honma, S.; Arase, A.; Itoh, M. *J. Am. Chem. Soc.* **1970**, *92*, 710.

(12) This interconversion was monitored by NMR spectroscopy in toluene-d_8.

(13) This phenomenon may exhibit substrate dependency and will be addressed in a more detailed study at a later date. For another example of competitive 1,2- and 1,4-additions to enones, see: Still, W. C.; Mitra, A. *Tetrahedron Lett.* **1978**, 2659.



aldehyde (1 equiv) furnished a solution of the aldol chelate **5a**.[14] Concomitant decomplexation of **5a** and elimination of phenylselenenic acid (H_2O_2, C_5H_5N, 0 °C to 30 °C, 1.5 h) provided the unsaturated aldol product **6a** in 67% yield.[15] This experimental protocol proved readily extendable to the representative acyclic α,β-unsaturated ketones (e.g., **2b,c**) to afford the corresponding ketols **6c–f** in excellent overall yields.[16a] Surprisingly, efforts to extend this procedure to 2-cyclohexen-1-one (**2d**) provided low yields of the ketols **6g,h**. This was attributed to the instability of the ketols toward chromatographic separation. This instability was substantially diminished by their conversion to the corresponding ketol acetates. Accordingly, oxidative decomplexation–elimination of the aldol adducts derived from enones **6a–d** followed by acetylation of the crude ketols (Ac_2O, C_5H_5N, 25 °C, 16 h) afforded the stable ketol acetates **7a–h** in good overall yields.[16b] In effect, the above operation represents a method for executing an aldol condensation at the nonenolizable α-carbon of an enone.[17] The results of a comprehensive study of various substrates are summarized in Table I.

As is evident from the results presented above, *B*-(phenylseleno)dialkylboranes (e.g., **1a**) are remarkably effective reagents for the aldol coupling of α,β-unsaturated ketones with aldehydes. The elucidation of additional synthetic applications of these reagents as well as the expression of the foregoing reaction in a chiral context (using the selenoborinate **1b**) will be the subjects of future reports.[20]

Acknowledgment. Financial support from the National Institutes of Health (GM 32000) is gratefully acknowledged. This manuscript is dedicated to the memory of Professor Robert V. Stevens.

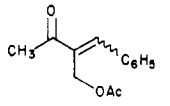
(14) Sequential treatment of the enone **2a** with **1a** and acetone under similar conditions produced a single stereoisomer (as evidenced by 300-MHz ^{1}H NMR), thus the relative stereochemistry of the product **5a** was assumed to be trans due to the facile elimination of phenylselenenic acid upon oxidation. A more thorough examination of the stereochemical outcome of the tandem condensation reactions is currently underway.

(15) All reported yields refer to chromatographically isolated, analytically pure products that exhibited satisfactory elemental analyses (C, H) and ^{1}H NMR (300 MHz) and IR spectra.

(16) (a) A representative experimental procedure for the synthesis of a ketol acetate is as follows: An oven-dried, one-necked flask equipped with a magnetic stirring bar, nitrogen inlet adaptor, and rubber septum was charged with 4.96 mL (0.605 M in $PhCH_3$) of 9-(phenylseleno)-9-borabicyclononane (3.0 mmol). To this was added 0.359 mL of freshly distilled 4,4-dimethyl-2-cyclopenten-1-one (3.0 mmol) at 25 °C. After stirring 2 h, 0.305 mL of benzaldehyde (3.0 mmol) was added, and the mixture was allowed to stir an additional hour. The reaction was then diluted with 25 mL of CH_2Cl_2 followed by the addition of 0.919 mL of 30% H_2O_2 (30.0 mmol) and 2.43 mL of C_5H_5N (30.0 mmol) at 0 °C. The reaction was warmed to 25 °C for 45 min, after which it was added to 125 mL of ether and sequentially extracted with 2 × 50 mL of 10% $KHCO_3$, 3 × 50 mL of 7% $CuSO_4$, 25 mL of water, and 50 mL of concentrated brine and then dried over $MgSO_4$. The solvent was evaporated and the crude mixture was chromatographed on 80 g of Brockmann 3 neutral alumina with 10% ethyl acetate/hexane to yield 0.4345 g (67%) of the unsaturated ketol as a white crystalline solid: NMR δ ($CDCl_3$/Me_4Si) 1.17 (s, 6 H, CH_3), 2.28 (s, 2 H, O=CCH_2), 3.45 (d, 1 H, J = 5.0 Hz, OH), 5.46 (dd, 1 H, J = 1.5, 5.0 Hz, HCO), 6.98 (d, 1 H, J = 1.5 H, C=CH), 7.30 (m, 5 H, Ar H); IR cm^{-1} (CCl_4) 3620 (w, OH) 3600–3300 (m, bd, OH), 3100–3000 (m, CH, unsaturated envelope), 1703 (vs, C=O). (b) The corresponding ketol acetate was produced by subjecting the crude reaction mixture arrived at by the above procedure to flash chromatography on 15 g of Brockmann 3 neutral alumina with 50% ethyl acetate/hexane. After solvent evaporation, the resultant yellow oil was dissolved in 16 mL of pyridine and 4 mL of acetic anhydride and stirred for 16 h. The excess acetic anhydride was decomposed with 3 mL of 85% lactic acid and the mixture was again worked up as described above. Medium pressure liquid chromatography on 200 g of Brockmann 3 neutral alumina with 10% ethyl acetate/hexane gave 0.5212 g (67%) of the unsaturated ketol acetate as a white crystalline solid: NMR δ ($CDCl_3$/Me_4Si) 1.20 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 2.11 (s, 3 H, O=CCH_3), 2.31 (s, 2 H, O=CCH_2), 6.55 (d, 1 H, J = 1.0 Hz, OCH), 7.23 (d, 1 H, J = 1.0Hz, C=CH), 7.30 (m, 5 H, Ph-H). IR cm^{-1} (CCl_4): 3100–3000 (m, C-H, unsaturated envelope), 1750 (vs, C=O, ester), 1715 (vs, C=O, ketone), 1225 (s, CC(=O)O).

(17) The utility of selenoalanes to effect this transformation has been reported (ref 6 and 7). Selenoalanes have been shown to be exceedingly reactive species which rapidly condense with many functional groups (e.g., esters, lactones, and epoxides) (ref 8). The selenoborinate **1a** has been revealed to be significantly more selective in this regard; esters, γ-lactones, and nitriles have been shown inert to **1a** over several hours at 25 °C.

(18) The product obtained in this instance was not the anticipated product but the rearranged ketol acetate **8**.



8

(19) The isomers were assigned on the basis of the following spectral data. **6e(E)**: IR cm^{-1} ($CDCl_3$) 3605 (w), 3470 (s, bd), 1635 (vs); NMR δ ($CDCl_3$/Me_4Si) 2.04 (d, 3 H, J = 7.3 Hz, C=CCH_3) 4.76 (d, 1 H, J = 10.2 Hz, OH), 5,86 (d, 1 H, J = 10.2 Hz, HCO), 6.53 (q, 1 H, J = 7.2 Hz, C=CH), 7.21–7.60 (m, 10 H, Ar H). Positive NOE observed between presaturated vinylic proton and aromatic protons and presaturated allylic methyl protons and aromatic and methine protons. **6e(Z)**: IR cm^{-1} ($CDCl_3$) 3605 (m), 3475 (w, bd), 1650 (vs); NMR ($CDCl_3$/Me_4Si) 1945 (dq, 3 H, J = 1.0, 7.3 Hz, C=CCH_3), 3.24 (d, 1 H, J = 5.1 Hz, OH), 5.55 (d, 1 H, J = 5.1 Hz, HCO), 6900 (d, 1 H, J = 1.0, 7.3 Hz, C=CH), 7.18–7.76 (m, 10 H, Ar H). Positive NOE observed between presaturated vinylic proton and aromatic and methine protons and presaturated allylic methyl protons and aromatic protons. **6f(E)**: IR cm^{-1} ($CDCl_3$) 3610 (w), 3480 (m, bd), 1625 (vs); NMR ($CDCl_3$/Me_4Si) 0.87 (d, 3 H, J = 6.6 Hz, CH_3), 1.12 (d, 3 H, J = 6.6 Hz, CH_3), 1.96 (d, 3 H, C=CCH_3), 2.05 (m, 1 H, HC), 4.2 (m, 2 H, HCO), 6.47 (q, 1 H, J = 7), 7.67–7.41 (m, 5 H, Ar H). Positive NOE observed between presaturated vinylic proton and aromatic protons. **6f(Z)**: IR cm^{-1} ($CDCl_3$) 3615 (m), 3490 (w, bd), 1640 (vs); NMR δ ($CDCl_3$)/Me_4Si) 0.94 (d, 3 H, J = 6.7 Hz, CH_3), 0.98 (d, 3 H, J = 6.7 Hz, CH_3), 1.55 (d, 1 H, J = 7.2 Hz, C=CCH_3), 1.80 (m, 1 H, HC), 2.62 (d, 1 H, J = 6.2 Hz, OH), 4.02 (dd, 1 H, J = 6.2, 6.2 Hz, HCO) 6.10 (dq, 1 H, J = 0.9, 7.2 Hz, C=CH), 7.43–7.95 (m, 5 H, Ar H). Positive NOE observed between presaturated vinylic proton and methine and hydroxyl protons and presaturated allylic methyl protons and aromatic protons.

(20) Preliminary reactions employing the selenoborinate **1b** have afforded product ketols in modest enantiomeric excesses. The stereoselectivity associated with this process is currently being optimized.

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