After considerable experimental probes,[10] the three most promising reagents identified for exploration were (*R*)- or (*S*)-bi-2-naphthol/$LiAlH_4$ (**3**, Binal-H, Noyori's reagent[14]), 1,2(*S*)-diphenyl-3(*R*)-methyl-4-(dimethylamino)-2-butanol/$LiAlH_4$ (**4**, Chirald/LAH, Mosher's reagent[15]), and potassium 9-*O*-(1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranosyl)-9-boratabicyclo[3.3.1]nonane (**5**, K 9-*O*-DIPGF-9-BBNH, Brown's reagent[1f]). The requisite imines **1**, chosen to incorporate a variety of structural features, were synthesized from the corresponding ketoximes and chlorodiphenylphosphine (eq 1).[7] In general, the reaction

$$R_1R_2C{=}NOH \xrightarrow[-40\ °C]{(C_6H_5)_2PCl} [R_1R_2C{=}NOP(C_6H_5)_2] \rightarrow \underset{\mathbf{1}}{R_1R_2C{=}NP(O)(C_6H_5)_2} \xrightarrow{\text{reduction}} \underset{\mathbf{2}}{R_1R_2CHNHP(O)(C_6H_5)_2} \quad (1)$$

conditions for reductions were initially chosen to mimic those found most successful for corresponding studies with ketones,[1f,14,15] except that shorter reaction times were found sufficient[8] (Tables I and II).

Reductive results with reagents **3**, **4**, and **5** for arylalkyl and methylalkyl derivatives of **1** are displayed in Tables I and II, respectively, along with comparisons (where known) with results for reductions of the corresponding ketones. Several significant features of the conversions are evident from the tables. Thus, in general, enantioselectivities obtained with dialkyl cases match or exceed the selectivities with arylalkyl examples, in contrast to results generally observed with ketones when these reagents are used.[1f,14,15] Furthermore, with all examples, control of the chiral sense displayed appears to depend roughly on the relative bulk of the groups flanking the imine and not on electronic interactions as postulated for some ketones.[14] This is particularly evident with reagent **5**. Thus, with **1a** (Table I, entry 5), very little distinction between phenyl and methyl is observed (15% ee). However, as the alkyl size increases, the chiral sense obtained changes (*R* to *S*) and the magnitude of enantioselectivity is enhanced (compare entries 5, 9 and 12, Table I). Likewise, increasing the effective bulk of the aryl group affords increased discrimination of constant chiral sense[16] (*R*, compare entries 5, 16, and 17, Table I). Apparently, aromatic rings (except α-naphthyl[16]) behave as relatively small groups that project an unencumbered flat orientation toward the encroaching reagent, and therefore the sense and degree of chiral recognition is controlled by the comparative size of the alkyl group.

With dialkyl groups, reagent **5** consistantly affords the *R* enantiomer predominately (as is obtained with ketones[1f]), and the magnitude of enantioselectivity is again controlled mostly by relative group sizes. *Significantly, the reductions of dialkyl derivatives of* **1** *with* **5** *represent the highest enantioselectivities (50–84% ee) obtained to date for the conversion of prochiral imine derivatives to chiral amines with hydride reagents.*

A further interesting feature of reductions of arylalkyl derivatives was observed with reagent **3** upon extended reaction times. Thus, with **1a**, **1b**, and **1d**, allowing the reactions to proceed for 24–70 h resulted in much lower chemical yields but concomitant dramatic relative enrichments of the major enantiomers (compare entries 1 vs. 2 and 3, 6 vs. 7, 13 vs 14; Table I). Evidently, kinetic asymmetric distruction selectively depletes the minor enantiomer. This curious and potentially useful kinetic resolution is currently under further investigation.

As mentioned, the procedures utilized were those found to proceed successfully for the reduction of ketones.[1f,14,15] The following procedure for the reduction of 1-cyclohexyl-*N*-(diphenylphosphinyl)ethanimine **1j** with reagent **5** is illustrative. To the *N*-diphenylphosphinyl imine **1j** (1.01 g, 3.1 mmol) in dry THF (10 mL) cooled to −78 °C under N_2 was added a solution of K 9-*O*-DIPGF-9-BBNH (**5**)[1f] (3.8 mmol). The mixture was stirred at −78 °C for 30 min and then quenched with 5% aqueous HCl. The mixture was extracted with ether which was dried ($MgSO_4$) and evaporated to obtain an oily residue (2.2 g). Flash column chromatography[19] on silica gel (CH_2Cl_2 followed by 5% THF/CH_2Cl_2) afforded the phosphinylamine **2j** (0.98 g, 95%; $[\alpha]^{25}_D$ −13.5° (*c* 10, CH_2Cl_2)) which represents an 84% ee based on comparison of a rotation of $[\alpha]^{25}_D$ −15.93° (*c* 10, C_2Cl_2) for an authentic sample prepared from a sample of the optically pure amine.

Further investigations including the preparation of chiral α-amino acids are currently under way.

(9) Greene, T. W. *Protective Groups in Organic Synthesis*; Wiley: New York, 1981; pp 281–282. (b) Kenner, G. W.; Moore, G. A.; Ramage, R. *Tetrahedron Lett.* **1976**, 4005. (c) Koziara, A.; Olejniczak, B.; Osowska, K.; Zwierzak, A. *Synthesis* **1982**, 918. (d) Cleavage of optically active *N*-(diphenylphosphinyl)amines with HCl affords the corresponding amines with no loss of optical purity.

(10) Ineffective reagents investigated include the trisubstituted boranes *B*-(3-pinanyl)-9-borabicyclo[3.3.1]nonane (ref 1d), nopol-9-BBN (ref 11), and diisopinocampheylchloroborane (ref 1e), which did not afford reduced products, the corresponding borohydrides from the former two reagents (ref 1a, 12, 13), and the chiral sulfamide/$LiAlH_4$ reagent (ref 1g), which gave good chemical yields but poor enantioselectivity (i.e., <10%).

(11) Midland, M. M.; Kazubski, A. *J. Org. Chem.* **1982**, *47*, 2814.

(12) Krishnamurthy, S.; Vogel, F.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 2534.

(13) Midland, M. M.; Kazubski, A. *J. Org. Chem.* **1982**, *47*, 2495.

(14) (a) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709. (b) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717.

(15) Yamaguchi, S.; Mosher, H. S. *J. Org. Chem.* **1973**, *38*, 1870.

(16) Repulsions between the α-naphthyl substituent and the ring peri-H twists the substituent out of plane which effectively enlarges the steric requirement of the ring compared to the β-naphthyl (or phenyl) ring.

(17) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(18) Johnson, C. R.; Elliott, R. C.; Penning, T. D. *J. Am. Chem. Soc.* **1984**, *106*, 5019.

(19) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(20) Present address: Wyeth Laboratories, West Chester, PA 19380.

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Novel Photochemical–Diradical Cyclization Methods for Protoberberine Alkaloid Synthesis. Preparation of (±)-Xylopinine and (±)-Stylopine

Summary: A new synthetic approach to members of the protoberberine alkaloid family based upon a photochemical–diradical cyclization methodology is described.

Sir: In recent years, a host of new approaches for carbocyclic and heterocyclic ring construction have grown out of mechanistic studies in the areas of radical and excited-state chemistry.[1,2] Our efforts in this area have focused

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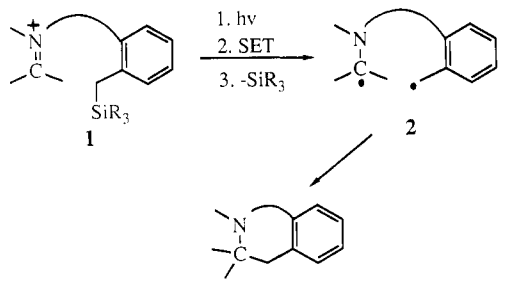
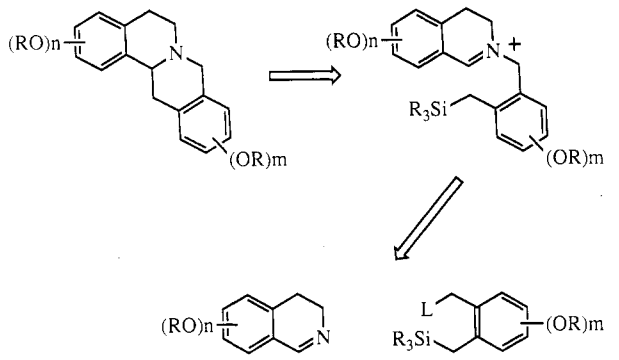
Scheme I



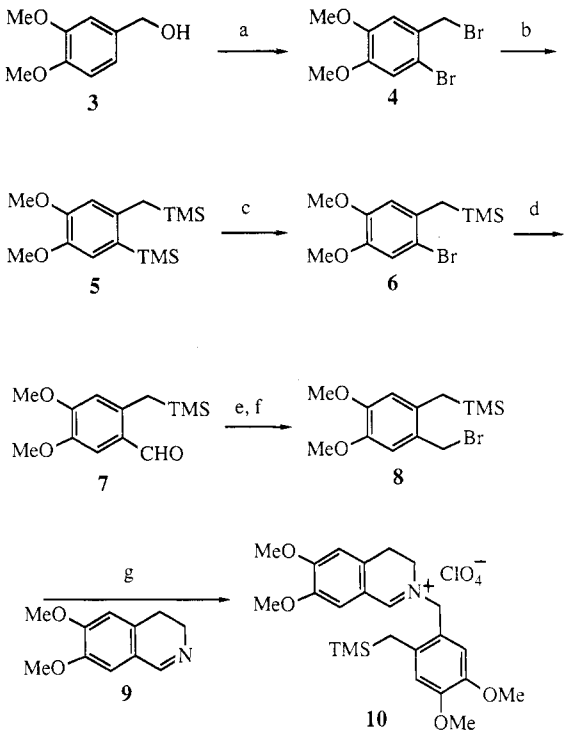
Scheme II



on the excited-state electron-transfer processes of donor–iminium salt acceptor systems. We have uncovered a variety of photocyclization processes which proceed via the intermediacy of diradicals.[3] Of particular interest in the context of the present studies are reactions of this type which are driven by electron-transfer–desilylation sequences and which occur in iminium salt–benzylsilane systems **1** (Scheme I).[4] In these cases, cyclization of diradical **2** results in carbon–carbon bond formation between the α-amino and benzylic radical centers.

The results of our preliminary studies of iminium salt–benzylsilane photochemistry have suggested that this process in intramolecular systems possesses the efficiency required for synthetic application.[4,5] In addition, their structural and functional outcomes appear to make reactions of this type suited as methods for isoquinoline alkaloid synthesis. In this paper we describe the results of investigations focusing on the application of this photochemical–diradical cyclization methodology as part of new strategies for the preparation of members of the protoberberine alkaloid family. The design employed is outlined in Scheme II and involves the convergent construction of the tetracyclic skeleton of these alkaloids by sequential N-alkylation and photocyclization starting with appropriately substituted 3,4-dihydroisoquinolines and silylmethylsubstituted benzyl halides. The utility of this strategy is demonstrated below by its application to the syntheses of the representative protoberberines (±)-xylopinine (**11**)[6] and (±)-stylopine (**20**).[7]

Scheme III



[a] (a) Br_2, HOAc, 25 °C, 95%; (b) Mg, Me_3SiCl, THF, 70%; (c) Br_2, CCl_4, 25 °C, 100%; (d) *n*-BuLi, THF, −78 °C, DMF, −78 °C, 83%; (e) $LiAlH_4$, Et_2O, 91%; (f) CBr_4, PPh_3, Et_2O, 75%; (g) $AgClO_4$, MeCN, 25 °C, 64%.

The dimethoxy(silylmethyl)benzyl bromide **8** used in the xylopinine approach was prepared beginning with the commercially available veratryl alcohol **3** by the sequence given in Scheme III. Dibromide **4**, produced from alcohol **3** by bromination,[8] was transformed to the bis-silyl derivative **5** through Grignard generation and Me_3SiCl trapping. Bromodesilylation[9] of **5** gave the aryl monobromide **6**[10] which was converted to the corresponding benzaldehyde **7** by formylation[6f] of the intermediate lithio compound. Reduction and bromination provided the desired benzyl bromide derivative **8**.

Silver perchlorate promoted alkylation of the known[11] 6,7-dimethoxy-3,4-dihydroisoquinoline (**9**) with bromide **8** gave the dihydroisoquinolinium perchlorate **10**[12] as a

(1) Giese, B *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon Press: Oxford, 1986.

(2) Gilbert, A. In *Synthetic Organic Photochemistry*; Horspool, W. M., Ed.; Plenum Press: London, 1984; Chapter 1, pp 1–60. Weedon, A. C., *Ibid.* Chapter 2, pp 61–144.

(3) Mariano, P. S. *Acc. Chem. Res.* **1983**, *16*, 130. Mariano, P. S. In *Synthetic Organic Photochemistry*, Horspool, W. M., Ed.; Plenum Press: London, 1984; Chapter 3, pp 145–258.

(4) Lan, A. J. Y.; Quillen, S. L.; Heuckeroth, R. O.; Mariano, P. S. *J. Am. Chem. Soc.* **1984**, *106*, 6439.

(5) Dai-Ho, G.; Lan, A. J. Y.; Mariano, P. S. *Tetrahedron Lett.* **1985**, *26*, 5867.

(6) For representative syntheses of xylopinine, see: (a) Bradsher, C. K.; Dutta, N. L. *J. Org. Chem.* **1961**, *26*, 2231. (b) Craig, L. E., Tarbell, D. S. *J. Am. Chem. Soc.* **1948**, *70*, 2783. (c) Battersby, A. R.; LeCount, D. J.; Garratt, S.; Thrift, F. J. *Tetrahedron* **1961**, *14*, 46. (d) Dyke, S. F.; Brown; D. W., Sainsbury, M.; Hardy, G. *Tetrahedron* **1971**, *27*, 3495. (e) Dutta, N. L.; Wadra, M. S.; Bundra, A. A. *Ind. J. Chem.* **1969**, *7*, 527. (f) Takano, S.; Numata, H.; Ogasawara, K. *J. Chem. Soc. Chem. Commun.* **1982**, 769. (g) Dean, R. T.; Rapoport, H. *J. Org. Chem.* **1978**, *43*, 2217. (h) Meyers, A. T.; Boes, M.; Dickinson, D. A. *Angew Chem., Int. Ed. Engl.* **1984**, *23*, 458.

(7) For representative syntheses of stylopine, see: (a) Haworth, R. D.; Perkin, W. H. *J. Chem. Soc.* **1926**, 1769; and ref 6a.

(8) Barthel, W. F.; Alexander, B. H. *J. Org. Chem.* **1958**, *23*, 1012.

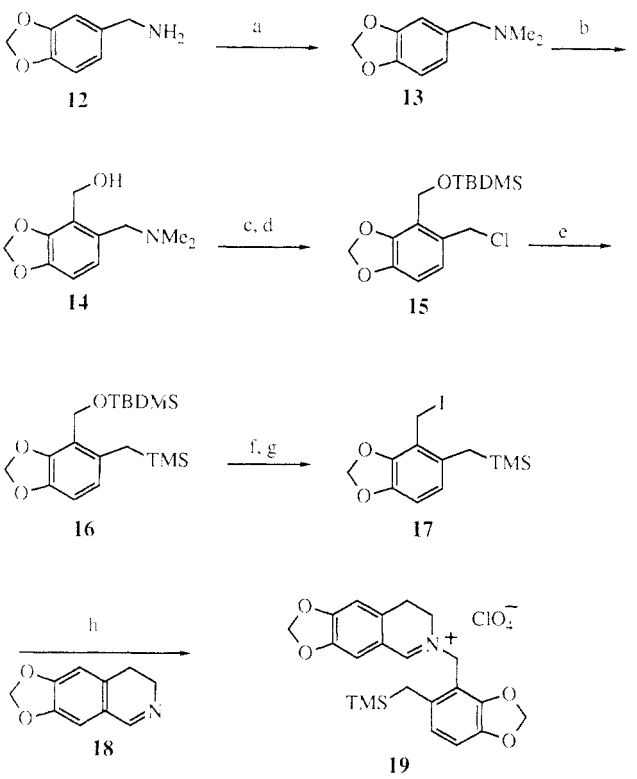
(9) Eaborn, G.; Walton, D. R. M.; Young, D. J. *J. Chem. Soc. B* **1969**, 15.

(10) An alternative one-step procedure involving monobenzylic silylation to produce the bromide **6** directly is less convenient to perform owing to the need to separate the bis-silyl compound **5**, whose formation cannot be avoided.

(11) (a) Dihydroisoquinolines **9**[11b] and **18**[11c] were prepared starting with the corresponding arylethylamines by using the N-formylation, $POCl_3$-induced cyclization procedure described by Whaley.[11d] (b) Buck, J. S.; Ide, W. S. *J. Am. Chem. Soc.* **1983**, *60*, 2101. (c) Decker, H.; Kropp, W.; Hayer, H.; Becker, P. *Ann.* **1913**, *395*, 299. (d) Whaley, W. M.; Govindachari, T. R. *Organic Reactions*; Wiley: New York, 1951; Vol. VI, Chapter 2.

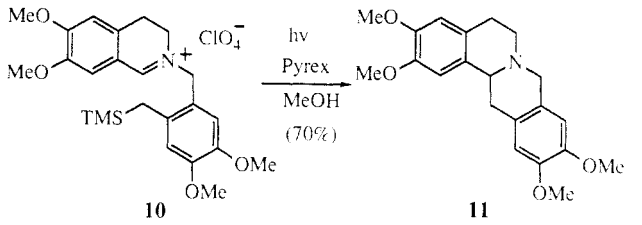
(12) The perchlorate anion was selected in order to avoid electron transfer between the excited hydroisoquinolinium cation and a more easily oxidized counterion.

Scheme IV



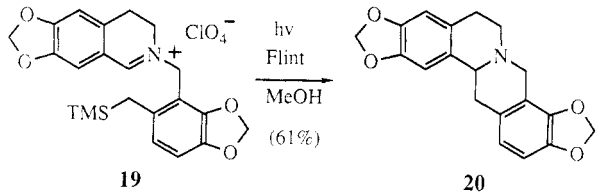
[a](a) HCHO, HCO_2H, 80 °C, 90%; (b) *n*-BuLi, 0 °C, THF/HCHO, −78 °C, 90%; (c) $(i\text{-Pr})_2EtN$, TBDMSCl, DMF, 98%; (d) $ClCO_2Et$, THF, 25 °C, 99%; (e) Mg, THF, Me_3SiCl, 46%; (f) 1 N H_2SO_4, THF, 25 °C, 93%; (g) I_2, PPh_3, DIPEA, 40%; (h) $AgClO_4$, MeCN, 25 °C, 70%.

crystalline substance (mp 176–178 °C, MeOH).[13] Irradiation (Pyrex, MeOH) of **10** led to smooth production of (±)-xylopinine (**11**) (mp 154–157 °C, EtOH; lit.[6c] mp 157–158 °C) in a 70% yield. The spectroscopic properties of the synthetic materials matched those previously reported.[6g,14]



The sequence (Scheme IV) developed for preparation of the benzyl iodide **17** employed in the stylopine synthetic route takes advantage of a procedure described by Rapoport[6g] for C-2 functionalization of (3,4-dialkoxybenzyl)-amines. Accordingly, the *N,N*-dimethylpiperonylamine **13**, formed by methylation[15] of the commercially available piperonylamine **12**, was converted by *n*-BuLi deprotonation and equilibration to the thermodynamically[16] more stable C-2 anion. Formaldehyde trapping generated the desired C-2 carbinol **14** (mp 89–90 °C, Et_2O). Deamination was then performed subsequent to protection of the hydroxyl function by treatment with $ClCO_2Et$. The benzylic chloride **15** formed in this fashion was converted to the silane **16** via in situ Me_3SiCl trapping of the corresponding Grignard. The alcohol function in **16** was then deprotected and transformed to the benzylic iodide found in the target substrate **17**.

The dihydroisoquinolinium perchlorate **19** needed for the photocyclization process was smoothly formed by silver perchlorate assisted alkylation of the known[11] methylenedioxy-3,4-dihydroisoquinoline **18**. The salt is furnished as a crystalline substance (mp 186–188 °C, $CHCl_3$). Photocyclization occurs upon irradiation of **19** (Flint, MeOH) to produce (±)-stylopine (**20**) (mp 213–215 °C, MeOH, lit.[6a] mp 217–218 °C) which has spectroscopic properties identical with those previously reported.[14]



The strategy described above for protoberberine alkaloid synthesis appears to rival in overall efficiency those followed in earlier synthetic approaches to this family.[6,7] Our studies focusing on the application of photochemical diradical cyclization methods for natural product synthesis are continuing.

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(13) A different sequence employing a Bischler–Napieralski cyclization has been used for synthesis of a salt related to **10**.[6f] We have found that the procedure described here is more efficient.

(14) Shamma, M.; Hindenlang, D. M. *Carbon-13 NMR Shift Assignments of Amines and Alkaloids*; Plenum: New York, 1979.

(15) Pine, S. H.; Sanchez, B. L. *J. Org. Chem.* **1971**, *36*, 829.

(16) Ranade, A. C.; Mall, R. S.; Bhide, S. R.; Metha, S. R. *Synthesis* **1976**, 123.

A Highly Selective Photoinduced Dimerization of Olefins Catalyzed by Alkylcobaloximes

Summary: Olefins having an α-methyl group were dimerized selectively in the presence of alkylcobaloxime as a catalyst under irradiation by a tungsten lamp.

Sir: Considerable attention has been paid to cobaloximes as a model for vitamin B_{12}.[1] The cobalt–carbon bond in alkylcobaloxime is known to cleave homolytically by the irradiation of visible light as in eq 1.[2] To investigate the photoactivated alkylcobaloxime is interesting with respect to the enzymic rearrangement catalyzed by adenosylcobalamin.

$$RCo^{III}(Hdmg)_2B \overset{h\nu}{\rightleftharpoons} [R^{\bullet} + Co^{II}(Hdmg)_2B] \quad (1)$$

Hdmg, dimethylglyoximato; B, base

(1) (a) Schrauzer, G. N. *Acc. Chem. Res.* **1968**, *1*, 97. (b) Golding, B. T.; Sell, C. S.; Sellars, P. J. *J. Chem. Soc., Perkin Trans. 2* **1980**, 961. (c) Flohr, H.; Pannhorst, W.; Retey, J. *Helv. Chim. Acta* **1978**, *61*, 1565. (d) Jensen, F. R.; Kiskis, R. C. *J. Am. Chem. Soc.* **1975**, *97*, 5825. (e) Tada, M.; Okabe, M.; Miura, K. *Chem. Lett.* **1978**, 1135.

(2) (a) Jensen, F. R.; Madan, V.; Buchandan, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 5283. (b) Schrauzer, G. N.; Lee, L. P.; Sibelt, J. W. *J. Am. Chem. Soc.* **1970**, *92*, 2997.

0022-3263/87/1952-0706$01.50/0