Pergamon

Tetrahedron Letters, Vol. 36, No. 17, pp. 2941-2944, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00443-2

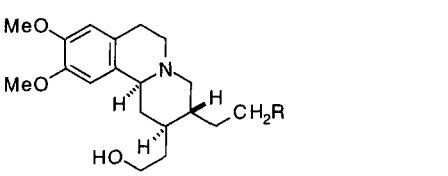
Catalytic Iron-Mediated Enediene Carbocyclizations: The Enantioselective Synthesis of a Homologue of the Alkaloid (-)-Protoemetinol

James M. Takacs* and Scott C. Boito

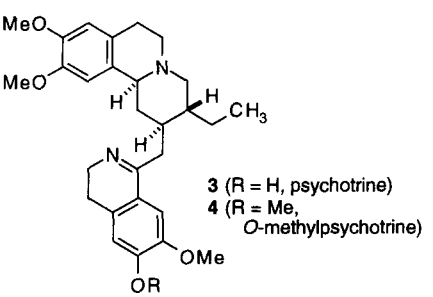
Department of Chemistry, University of Nebraska-Lincoln, Lincoln NE 68588-0304

Summary: The efficient enantioselective synthesis of the benzoquinolizidine **2** highlights the utility of the stereoselective iron-catalyzed cyclization of enedienes and affords the opportunity to prepare analogues of protoemetinol, psychotrine, and related natural products.

(-)-Protoemetinol is a benzo[a]quinolizidine alkaloid isolated from *Alangium lamarckii* by Battersby and coworkers.[1] It is structurally related to a number of alkaloids isolated from species within the *Alangiaceae* plant family (*e.g.*, psychotrine (**3**), emetine, cephaeline, and tubulosine), many of which are also constituents of ipecacuanha plants within the *Rubiaceae* family. These two plant families have attracted interest due to their use as folk remedies for a variety of aliments, and a number of their benzoquinolizidine constituents have exhibited potent biological activity.[2] For example, it was recently reported that psychotrine (**3**) and *O*-methylpsychotrine (**4**) are potent inhibitors of HIV-1 reverse transcriptase[3] and exhibit an unusual four-fold more potent inhibition of HIV-2 RT (9-10 μM) compared to HIV-1 RT.[4]



1 (R = H, (-)-protoemetinol)
2 (R = CH_3)

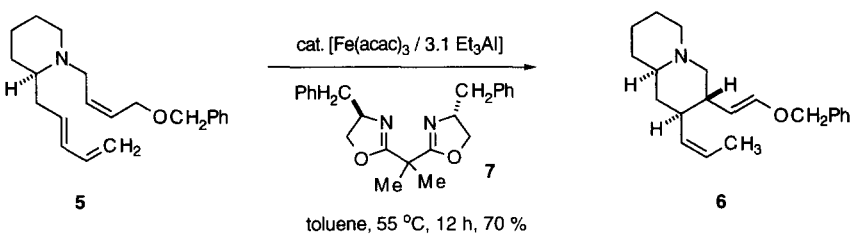


3 (R = H, psychotrine)
4 (R = Me, *O*-methylpsychotrine)

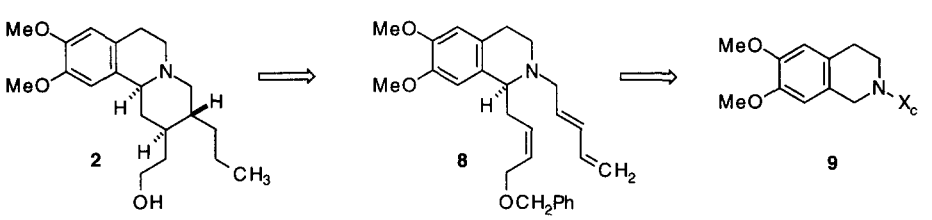
(-)-Protoemetinol (**1**) and its analogues are attractive synthetic targets. The convergent disconnection of pyschotrine (**3**), as well as *O*-methylpsychotrine (**4**), emetine, cephaeline, tubulosine and related alkaloids, reveals the protoemetinol structure as essentially constituting the upper half of the molecule. A number of enantioselective syntheses of molecules within this class of alkaloids proceed via the intermediacy of protoemetinol.[5-9]

We are involved in the development of novel cyclization methods that exploit catalytic metal-mediated reactions. Given its abundance and low toxicity, iron is an attractive metal for developing methods for organic synthesis.[10-13] We have defined several stereoselective cyclization modes of enediene (triene) substrates effected by catalytic iron chemistry.[14-17] For example, enediene **5** undergoes iron-catalyzed cycloisomerization

to afford the substituted quinolizidine **6** in good yield (70 %) and with a reasonable level of stereoinduction (6:1 mixture of two diastereomers obtained).[18] The iron catalyst is generated in situ via the reduction of ferric acetylacetonate ($Fe(acac)_3$) with 3.1 equivalents of triethylaluminum. A bidentate nitrogen ligand (*e.g.*, **7**) is added as a modifier of the reduced iron catalyst.

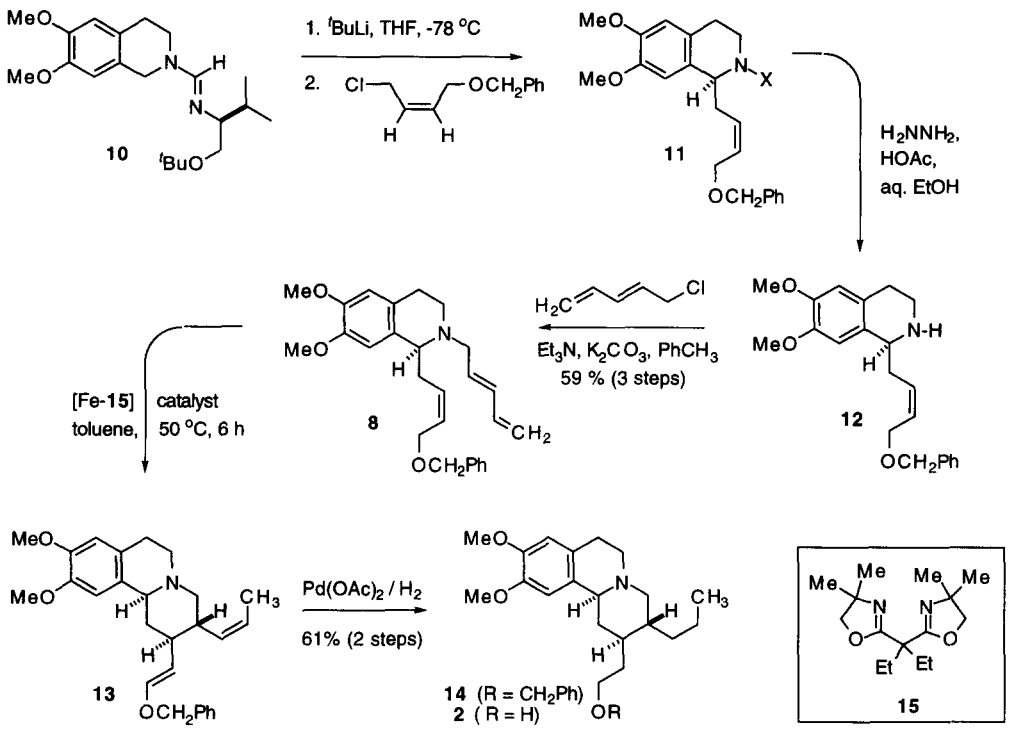


Several aspects of this cyclization are of particular note. First, there are relatively few reports of metal-mediated carbocyclizations of substrates bearing a basic nitrogen,[19-21] but that functionality is apparently well-tolerated in the iron-catalyzed cyclization of **5**. Secondly, the level of 1,3-stereoinduction from the resident stereocenter in substrate **5** depends on the ligand employed. A bipyridine-modified iron catalyst afforded a 3:2 mixture of diastereomers, while the chiral bisoxazoline **7** gave an enhanced level of 1,3-stereoinduction affording the 6:1 mixture of diastereomers. We reasoned that these observations could be exploited for the facile synthesis of benzoquinolizidine **2**, a one carbon homologue of (-)-protoemetinol. The retrosynthetic analysis is shown below. Compound **2** was expected to arise via the iron-catalyzed cyclization of enediene **8** and subsequent hydrogenation/debenzylation of the cyclized product. Scalemic **8** would be prepared via the diastereoselective alkylation of a suitable chiral tetrahydroisoquinoline derivative **9**.



The synthesis was accomplished as illustrated in scheme 1. Meyers and coworkers[22] have devised an efficient method for the highly diastereoselective alkylation of chiral tetrahydroisoquinolines bearing a formamidine auxiliary derived ultimately from (*R*)- or (*S*)-valinol. Subsequent removal of the formamidine chiral auxiliary affords substituted tetrahydroisoquinolines in high enantiomeric purity. For example, Meyers reported that treatment of the anion derived from the chiral formamidine derivative of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (compound **10**) with methyl iodide followed by removal of the chiral auxiliary by treatment with hydrazine affords (-)-salsolidine in 60 % overall yield and 95 % *ee*.[23] The deprotonation of **10** using *tert*-butyllithium (THF, -78 °C, 15 min) and alkylation of the resulting anion with (*Z*) 1-chloro-4-benzyloxy-2-butene[24] (1. -78 °C, 3 h; 2. extractive workup) affords compound **11a** (X = CH=NCH(^{i}Pr)CH_2O^tBu). Without further purification, the chiral auxiliary was removed as per the Meyers protocol[23] by treatment with hydrazine in acidic aqueous ethanol (1:13:20 HOAc:H_2O:EtOH, 25 °C, 12 h).

Scheme 1. The enantioselective synthesis of benzoquinolizidine **2**.



After extractive workup, *O-t*-butylvalinol was recovered by distillation from the crude reaction mixture (bp ≤ 60 °C, 0.1 torr) and the residue (predominantly **12**) carried on without further purification. The enantiomeric purity of **12** was established to be greater than 92 % *ee* by its conversion to the corresponding naphthamide derivative **11b** (X = (1-naphthyl)C(O)-) and analysis by chiral HPLC.[25] To complete the enediene synthesis, the secondary amine **12** was *N*-alkylated with pentadienyl chloride (Et_3N, K_2CO_3, toluene, 50 °C, 18 h). After chromatographic purification, enediene **8** was obtained in three steps and 59 % overall yield from compound **10**.

Treatment of enediene **8** with a bisoxazoline-modified iron catalyst (0.14 eq [$Fe(acac)_3$ / 1.1 bisoxazoline **15** / 3.1 Et_3Al], toluene, 50 °C, 6 h) afforded **13**. Purification at this stage proved problematic due to the labile enol ether functionality, but analysis of the relevant vicinal coupling constants extracted from the ^1H NMR spectrum of the crude product unambiguously established the stereochemistry as depicted in structure **13**. At this point all that remained was reduction of the two double bonds followed by reductive cleavage of the benzyl ether moiety. Rhodium-catalyzed hydrogenation of crude **13** (5 % Rh on Al_2O_3, H_2 (1 atm), 97:3 MeOH:$CHCl_3$, 25 °C, 20 h) afforded the reduced, but not debenzylated product **14** . NMR and HPLC analysis of **14** (Hibar LiChrosorb Si60, 95:5 Hex:i-PrOH, 2.0 mL/min) indicated that the iron-catalyzed cyclization proceeded with a high level of stereoinduction (greater than 96 % *de*). **14** could be subsequently debenzylated,

but the one-pot palladium-catalyzed reduction and debenzylation of crude **13** (0.6 eq $Pd(OAc)_2$, H_2 (1 atm), 97:3 MeOH:$CHCl_3$, 25 °C, 20 h) proved more efficient and afforded purified **2**[26] in 61 % yield for the two steps from enediene **8** .

In summary, compound **2**, a one carbon homologue of the benzoquinolizidine (-)-protoemetinol, was synthesized in five steps and 36 % overall yield from **10** with just two chromatographic purifications. This efficient, enantioselective synthesis highlights the utility of the iron-catalyzed enediene cyclization and affords the opportunity to prepare analogues of psychotrine and related natural products.

Acknowledgments. Financial support of this work by the National Institutes of Health (GM34927) is gratefully acknowledged. We thank the NIH (SIG 1-S10-RR06301) for NMR instrumentation funding and the NSF (CHE-93000831) for GC-MS instrumentation funding.

References and Notes

(1) Battersby, A. R.; Kapil, R. S.; Bhakuni, B. S.; Popli, S. P.; Merchant, J. R.; Salgar, S. S. *Tetrahedron Lett.* **1965**, 4965-71.
(2) Fujii, T.; Ohba, M. in *The Alkaloids*; A. Brossi, ed.; Academic Press, Inc.: New York, 1983; Vol. 22; pp 1.
(3) Tan, G. T.; Kinghorn, A. D.; Hughes, S. H.; Pezzuto, J. M. *J. Biol. Chem.* **1991**, *266*, 23529-36.
(4) Tan, G. T.; Miller, J. F.; Kinghorn, A. D.; Hughes, S. H.; Pezzuto, J. M. *Biochem. Biophys. Res. Commun.* **1992**, *185*, 370-8.
(5) Ihara, M.; Yasui, K.; Taniguchi, N.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1469-76.
(6) Ihara, M.; Yasui, K.; Taniguchi, N.; Fukumoto, K.; Kametani, T. *Tetrahedron Lett.* **1988**, *29*, 4963-6.
(7) Hirai, Y.; Terada, T.; Hagiwara, A.; Yamazaki, T. *Chem. Pharm. Bull.* **1988**, *36*, 1343-50.
(8) Bhattacharjya, A.; Mukhopadhyay, R.; Sinha, R. R.; Ali, E.; Pakrashi, S. C. *Tetrahedron* **1988**, *44*, 3477-88.
(9) Fujii, T.; Ohba, M.; Yoshifuji, S. *Heterocycles* **1988**, *27*, 1009-32.
(10) Pearson, A. J.; Shively, R. J., Jr. *Organometallics* **1994**, *13*, 578-84.
(11) Sigman, M. S.; Kerr, C. E.; Eaton, B. E. *J. Am. Chem. Soc.* **1993**, *115*, 7545-6.
(12) Tao, C.; Donaldson, W. A. *J. Org. Chem.* **1993**, *58*, 2134-43.
(13) Rigby, J. H.; Ogbu, C. O. *Tetrahedron Lett.* **1990**, *31*, 3385-8.
(14) Takacs, J. M.; Myoung, Y.-C.; Lawrence G, A. *J. Org. Chem.* **1994**, *59*, 6928-42.
(15) Takacs, J. M.; Myoung, Y. C. *Tetrahedron Lett.* **1992**, *33*, 317-320.
(16) Takacs, B. E.; Takacs, J. M. *Tetrahedron Lett.* **1990**, *31*, 2865-8.
(17) Takacs, J. M.; Newsome, P. W.; Kuehn, C.; Takusagawa, F. *Tetrahedron* **1990**, *46*, 5507-5522.
(18) Takacs, J. M.; Weidner, J. J.; Takacs, B. E. *Tetrahedron Lett.* **1993**, *34*, 6219-6222.
(19) Hong, C. Y.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028-9.
(20) Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *111*, 6478-80.
(21) Trost, B. M.; Chen, S.-F. *J. Am. Chem. Soc.* **1986**, *108*, 6053-4.
(22) Meyers, A. I.; Dickman, D. A.; Boes, M. *Tetrahedron* **1987**, *43*, 5095-5108.
(23) Meyers, A. I.; Boes, M.; Dickman, D. A. *Org. Synth.* **1988**, *67*, 60.
(24) (*Z*) 1-chloro-4-benzyloxy-2-butene: CAS registry number 107691-95-2. For a preparation, see: Yadav, J. S.; Reddy, P. S. *Synth. Commun.* **1986**, *16*, 1119-31.
(25) HPLC analysis (Pirkle DNBPG chiral, 75:25 Hex:i-PrOH, 2.5 mL/min) showed peaks at 6.2 min ((*R*)-**11b**, 3.6 %) and 7.4 min ((*S*)-**11b**, 96.4 %). A sample of predominantly (*R*)-**11b** was prepared in via the sequence outline in scheme 1, but starting with the chiral formamidine derived from (*R*)-valinol.
(26) **2**: Capillary GC-MS analysis (30 m methylsilicone, CI mode) 23.0 min (98 % of the total peak area, base peak (M+1) at m/z 334; $[\alpha]_D$ -14.7° (c = 1.3, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 6.66 (s, 1H), 6.54 (s, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.76-3.67 (m, 1H), 3.63 (dd, J = 6.9, 7.1 Hz, 1H), 3.14-3.08 (m, 1H), 3.01 (dd, J = 3.9, 11.5 Hz, 2H), 2.95-2.92 (m, 1H), 2.59 (d, J = 16.2 Hz, 1H), 2.44 (dt, J = 4.1, 11.5 Hz, 1H), 2.31 (d, J = 12.9 Hz, 1H), 1.99 (t, J = 11.0 Hz, 1H), 1.95-1.87 (m, 1H), 1.58-1.47 (m, 2H), 1.45-1.36 (m, 2H), 1.27-1.20 (m, 2H), 1.17 (t, J = 6.9 Hz, 1H), 1.10-1.00 (m, 1H), 0.89 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.3, 147.0, 129.8, 126.5, 111.3, 108.1, 62.5, 61.6, 60.2, 56.0, 55.7, 52.3, 39.5, 37.9, 37.1, 35.8, 33.2, 29.0, 19.8, 14.4; Combustion analysis ($C_{20}H_{31}NO_3$ = 72.04 % C, 9.37 % H) found 72.16 % C, 9.41 % H.

(*Received in USA* 1 *February* 1995; *revised* 1 *March* 1995; *accepted* 3 *March* 1995)