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Asymmetric synthesis of (+)-loline

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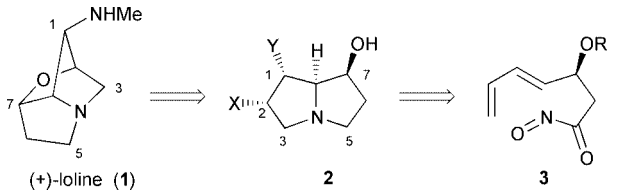
The first asymmetric synthesis of (+)-loline has been achieved in 20 steps from (−)-malic acid by a route incorporating intramolecular hetero-Diels–Alder cycloaddition of an acylnitrosodiene.

The lolium alkaloids comprise a small group of pyrrolizidine bases which possess a unique ether linkage bridging C2 and C7.[1] The principal member of the lolium group, (+)-loline **1**, was first isolated in 1955 from the rye grass *Lolium cuneatum* and its structure was initially misassigned.[2] Subsequently, lolium alkaloids were also found in the pasture grass tall fescue (*Festuca arundinacea*),[3] and most recently have been discovered in the roots of the tropical liana *Argyreia mollis*.[4] Acylated derivatives of loline are toxic to larvae of the horn fly (*Haematobia irritans*), an important arthopod ectoparasite of cattle.[5] A previous synthesis of (±)-loline **1** was reported in 1986 by Tufariello *et al.*[6]

Our plan for the synthesis of (+)-**1** envisioned formation of the bridging ether of loline at a late stage from a suitably functionalized pyrrolizidine core **2** (Scheme 1). Appropriate substituents X and Y could, in principle, be installed by oxidation of an unsaturated pyrrolizidine precursor. The latter was envisioned from a 3,6-dihydro-1,2-oxazine, itself accessible *via* intramolecular hetero-Diels–Alder cycloaddition of acylnitrosodiene **3**. Acylnitroso compounds are highly reactive dienophiles[7] and their cycloaddition chemistry has been exploited in several pyrrolizidine[8] and indolizidine[9] alkaloid syntheses.

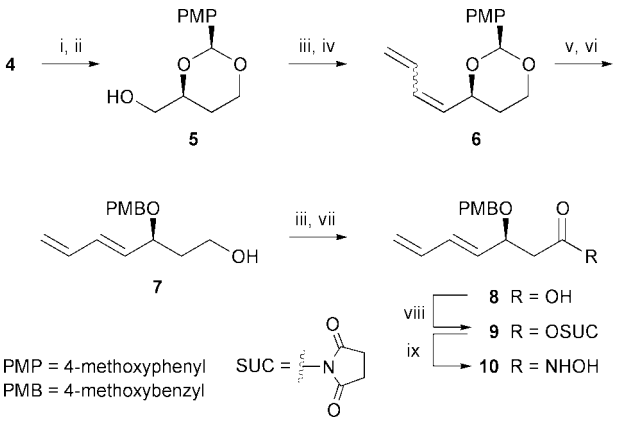
The synthesis of a suitable precursor for **3**, hydroxamic acid **10**, began with (*S*)-(−)malic acid **4** (Scheme 2). Conversion of **4** to diene **7** was accomplished in six steps by modification of an existing route to the analogous (*R*)-benzyl ether.[10] Thus, reduction of **4** with $BH_3{\cdot}SMe_2$ was followed by acid catalyzed acetalization of the resulting triol to yield dioxane **5**, $[\alpha]_D^{23}$ + 9.9 (*c* 0.96, $CHCl_3$), as a single diastereoisomer in 64% overall yield. Swern oxidation of the remaining free hydroxy group yielded an unstable aldehyde which was immediately reacted with allylidene triphenylphosphorane to afford diene **6** (*E*:*Z* = 3:7) in 40% yield (two steps). Since only two isomers were observable in both the ^{1}H and ^{13}C NMR spectra of **6** it was concluded that no epimerization of the aldehyde had occurred during the Wittig reaction. Treatment of **6** with 5 equivalents of DIBAL-H selectively reduced the less hindered acetal C–O bond to yield a primary alcohol with concomitant formation of an internal *p*-methoxybenzyl ether. Subsequent iodine (1 mol%) catalyzed photoisomerization (medium pressure mercury lamp, no filter) yielded diene **7** (63% from **6**), $[\alpha]_D^{23}$ −60.3 (*c* 1.10, $CHCl_3$), with *E*:*Z* ≥ 95:5 by ^{1}H NMR analysis. A second Swern oxidation gave an aldehyde which was further oxidized to the carboxylic acid **8** with buffered sodium chlorite. The latter was converted to *O*-succinimidyl ester **9**, and the activated ester was then amidated with hydroxylamine to yield hydroxamic acid **10**, $[\alpha]_D^{23}$ −30.2 (*c* 0.97, $CHCl_3$), in 75% overall yield from **7**.[9a]



Scheme 1

Initial studies of the hetero-Diels–Alder reaction were carried out with the protected hydroxamic acid **12**, previously prepared from diacetone-D-glucose.[11] Oxidation of **12** with a periodate salt generates a highly reactive acylnitroso intermediate which is trapped by the pendant diene to afford a mixture of the diastereomeric oxazines, **13*c*** and **13*t***. A range of reaction conditions for **12** was surveyed in the hope that good selectivity for the desired *cis* oxazine **13*c*** could be achieved (Table 1). Initial results in non-polar solvents were encouraging (entries 1–3) in that **13*c*** was the major product of the cycloaddition; however, the yield and selectivity were only moderate. Changes in temperature generally had little effect, although carrying out the reaction in refluxing benzene (entry 4) improved the overall yield at the expense of *cis* selectivity. The latter conditions are similar to those employed in the dienophile transfer technique reported by Keck and Nickell,[8] which gave very similar results. More polar solvents (entries 5–7) afforded better yields, but the reaction was not selective. Addition of water to the reaction medium resulted in a preference for the unwanted *trans* oxazine **13*t*** (entry 8); the effect of water on selectivity in an analogous reaction was noted previously by Kibayashi and coworkers.[10] The most practical conditions for preparation of **13*c*** (entry 7), when applied to **10** (entry 9), gave a 57:43 mixture of **11*c***:**11*t***. The oxazines **11*c***, $[\alpha]_D^{23}$ + 86.0 (*c* 0.71, $CHCl_3$), and **11*t***, $[\alpha]_D^{23}$ −75.5 (*c* 2.45, $CHCl_3$), were readily separated by silica gel chromatography.

Conversion of oxazine **11*c*** into pyrrolizidine lactam **14** was readily accomplished in three steps (Scheme 3). Reductive scission of the N–O bond of **11*c*** with excess sodium amalgam afforded a monocyclic allylic alcohol in 91% yield. After quantitative mesylation of the hydroxy group, exposure to LDA resulted in smooth cyclization to bicycle **14** (88%), mp 55–56 °C, $[\alpha]_D^{23}$ −72.0 (*c* 0.50, $CHCl_3$), upon warming.



Scheme 2 *Reagents and conditions*: i, $BH_3{\cdot}SMe_2$, $B(OMe)_3$, THF, 0 °C to r.t.; ii, $PMPCH(OMe)_2$, PPTS, CH_2Cl_2, reflux; iii, $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C, then Et_3N, −60 °C to r.t.; iv, allyltriphenylphosphonium bromide, BuLi, THF, −30 °C to r.t.; v, DIBAL-H, CH_2Cl_2, 0 °C to r.t.; vi, I_2, *hν*, C_6H_6, r.t.; vii, $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, 2-methylbut-2-ene, Bu^tOH–H_2O, 0 °C to r.t.; viii, CF_3CO_2SUC, Py, THF, r.t.; ix, $HONH_2{\cdot}HCl$, Et_3N, CH_2Cl_2, 0 °C.

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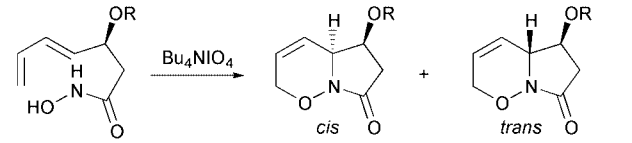
Table 1 Effect of solvent and temperature on the intramolecular hetero-Diels–Alder reaction of acylnitrosodienes[a] to yield 3,6-dihydro-1,2-oxazines



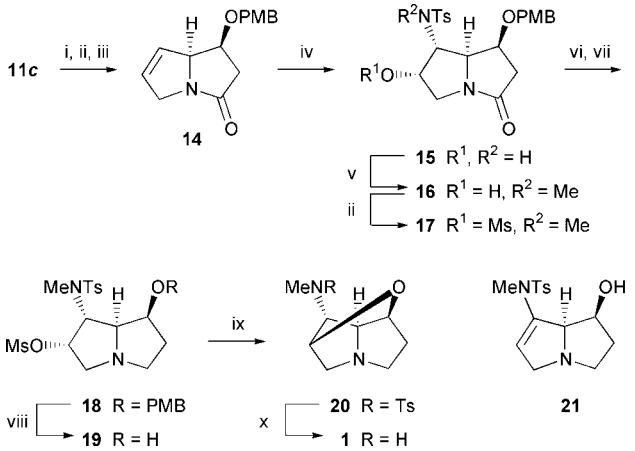
10 R = PMB
12 R = TBDMS

11c R = PMB
13c R = TBDMS

11t R = PMB
13t R = TBDMS

Entry	R	Solvent	*T*/°C	Yield[c] (%)	*Cis*:*trans*[d]
1	TBDMS	PhMe	−20	49	70:30
2	TBDMS	C_6H_6	0	60	71:29
3	TBDMS	C_6H_6	22	64	70:30
4	TBDMS	C_6H_6	80	80	60:40
5	TBDMS	CH_2Cl_2	−78	86	50:50
6	TBDMS	CH_2Cl_2	0	73	45:55
7	TBDMS	$CHCl_3$	22	91	55:45
8[b]	TBDMS	THF–H_2O (1:1)	0	97	27:73
9	PMB	$CHCl_3$	22	87	57:43

[a] The acylnitroso intermediate was generated *in situ* by slow addition of the hydroxamic acid (**10** or **12**) to a solution of $Bu^n_4NIO_4$ (2 equiv., *ca.* 0.03 M). [b] $NaIO_4$ used. [c] Isolated yield of oxazine products. [d] Determined by ^1H NMR integration of the mixture.



Scheme 3 *Reagents and conditions*: i, 6% Na(Hg), NaH_2PO_4, EtOH, 0 °C; ii, MsCl, Et_3N, CH_2Cl_2, 0 °C; iii, LDA, THF, −78 °C to r.t.; iv, $K_2OsO_2(OH)_4$, $(DHQD)_2PHAL$, chloramine-T, Bu^tOH-H_2O (1:1), r.t.; v, MeI, Bu^tOK, Bu^tOH, 50 °C; vi, $BH_3{\cdot}SMe_2$, THF, r.t.; vii, $Pd(OH)_2/C$, MeOH, r.t.; viii, DDQ, CH_2Cl_2–H_2O (20:1), r.t.; ix, *o*-$Cl_2C_6H_4$, 180 °C; x, sodium naphthalenide, DME, −60 °C.

Exploratory attempts to functionalize the olefinic bond of **14** led us to the discovery that **14** could be aminohydroxylated with the desired regioselectivity under the conditions used by Chang and Sharpless.[12] Thus, treatment of a mixture of **14** and chiral ligand $(DHQD)_2PHAL$ (25 mol%) in Bu^tOH–H_2O (1:1) with chloramine-T (2 equiv.), followed by portionwise addition of potassium osmate (1 mol% every 24 h for 3 days), afforded 40–52% of readily separated amino alcohols, **15** and its regioisomer, in a ratio of 3:1, respectively, together with 21% of a diol. All products were the result of oxidation of **14** from the *exo* face.

Selective methylation of the sulfonamide NH of **15** yielded 76% of **16**, $[\alpha]_D^{23}$ + 49.0 (*c* 0.55, $CHCl_3$); mesylation of the free alcohol then gave a 99% yield of the crystalline lactam **17**, mp 187–190 °C, $[\alpha]_D^{23}$ + 66.1 (*c* 0.70, $CHCl_3$). The latter was reduced with a large excess of $BH_3{\cdot}SMe_2$ (30 equiv.), and the resulting pyrrolizidine–borane complex was decomposed by the combined action of Pearlman's catalyst and methanol to give **18**, $[\alpha]_D^{23}$ + 73.3 (*c* 0.51, $CHCl_3$), in 73% overall yield. Oxidative removal of the PMB ether of **18** with DDQ was sluggish and required over 60 h to afford **19**, mp 175 °C (decomp.), $[\alpha]_D^{22}$ + 45.8 (*c* 0.28, $CHCl_3$), in 70% yield.

Unexpectedly, **19** failed to cyclize to the cage structure of loline under a variety of basic reaction conditions, giving only the elimination product **21** instead. In contrast, direct thermolysis of the hydroxy mesylate in the absence of a base afforded *N*-tosylloline **20**, $[\alpha]_D^{22}$ + 40.9 (*c* 0.11, $CHCl_3$), in 74% yield with no trace of **21**. *N*-Tosylloline prepared by tosylation of a sample of natural loline had $[\alpha]_D^{22}$ +38.0 (c 0.10, $CHCl_3$). Reductive removal of the tosyl substituent from **20** was effected with sodium naphthalenide and afforded (+)-loline **1**, isolated as its dihydrochloride salt in 48% yield. The ^1H and ^{13}C NMR spectra of synthetic material matched exactly those reported for the natural material.[13]

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Notes and references

1 L. P. Bush, F. F. Fannin, M. R. Siegel, D. L. Dahlman and H. R. Burton, *Agric., Ecosystems Environ.*, 1993, **44**, 81.
2 S. Y. Yunusov and S. T. Akramov, *J. Gen. Chem. USSR (Engl. Transl.)*, 1955, **25**, 1765; S. Y. Yunusov and S. T. Akramov, *J. Gen. Chem. USSR (Engl. Transl.)*, 1960, **30**, 3105.
3 S. G. Yates and H. L. Tookey, *Aust. J. Chem.*, 1965, **18**, 53.
4 B. Tofern, M. Kaloga, L. Witte, T. Hartmann and E. Eich, *Phytochemistry*, 1999, **51**, 1177.
5 C. T. Dougherty, F. W. Knapp, L. P. Bush, J. E. Maul and J. Van Willigen, *J. Med. Entomol.*, 1998, **35**, 798.
6 J. J. Tufariello, H. Meckler and K. Winzenberg, *J. Org. Chem.*, 1986, **51**, 3556.
7 For a review of acylnitroso compounds, see: G. W. Kirby, *Chem. Soc. Rev.*, 1977, **6**, 1.
8 G. E. Keck and D. G. Nickell, *J. Am. Chem. Soc.*, 1980, **102**, 3632; G. E. Keck, *Tetrahedron Lett.*, 1978, 4767.
9 For some examples, see: (*a*) G. E. Keck and D. R. Romer, *J. Org. Chem.*, 1993, **58**, 6083; (*b*) C. Kibayashi and S. Aoyagi, *Synlett*, 1995, 873; (*c*) H. Abe, S. Aoyagi and C. Kibayashi, *Tetrahedron Lett.*, 2000, **41**, 1205.
10 M. Naruse, S. Aoyagi and C. Kibayashi, *J. Org. Chem.*, 1994, **59**, 1358.
11 S. Kim and J. D. White, unpublished results.
12 G. Li, H.-T. Chang and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 451.
13 R. J. Petroski, S. G. Yates, D. Weisleder and R. G. Powell, *J. Nat. Prod.*, 1989, **52**, 810.