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AN ALTERNATIVE ENANTIOSELECTIVE TOTAL SYNTHESIS OF (+)-MONOMORINE I

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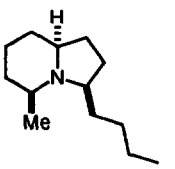
Abstract: An alternative enantioselective total synthesis of (+)-monomorine I has been achieved, based on asymmetric nitrone cycloaddition using a chiral allyl ether.

(+)-Monomorine I [(+)-**1**], isolated from Pharaoh's ant *Monomorium pharaonis*,[1] is the first example of indolizidine derivatives found in the animal kingdom and constitutes, together with other alkaloids found in thief ants, *Solenopsis* species, a rare group of anthropod alkaloids consisting of the indolizidine skeleton.[2] Due to its trail-following activity as well as unique structural feature, **1** has been the subject of extensive synthetic efforts which have culminated in numerous syntheses of racemic **1**[3] and a chiral synthesis of the unnatural enantiomer (–)-**1**.[4] Recently the first chiral synthesis of natural (+)-**1** has been reported from this laboratory.[5] In the present report we describe an alternative enantioselective synthesis of (+)-**1** by means of asymmetric 1,3-dipolar cycloaddition of a nitrone by using a chiral allyl ether as a dipolarophile.



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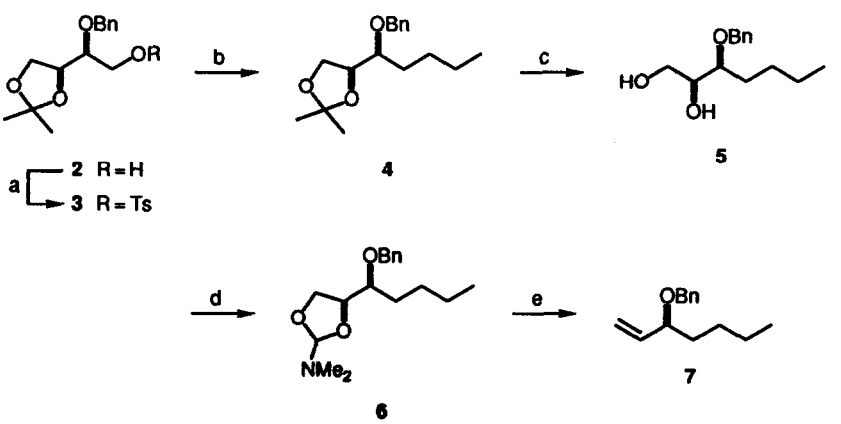
The L-threitol derivative **2**, prepared from diethyl L-tartrate,[6] was converted to the tosylate **3**[7] (97%), which underwent coupling with PrMgBr catalyzed by Li_2CuCl_4 to give **4** in 85% yield (Scheme I). Removal of

Scheme I

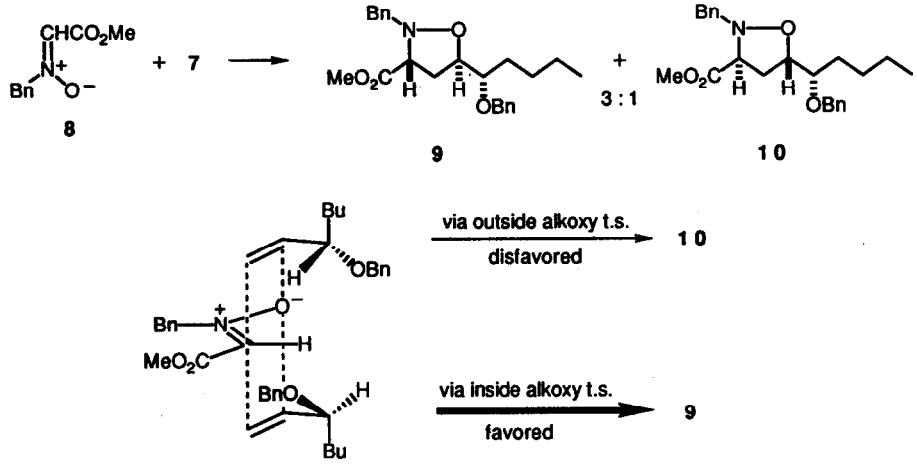


(a) TsCl, DMAP, CH_2Cl_2; (b) PrMgBr, Li_2CuCl_4, THF, –78 °C → room temperature; (c) 1 N HCl, MeOH; (d) $Me_2NCH(OMe)_2$; (e) Ac_2O, 190 °C.

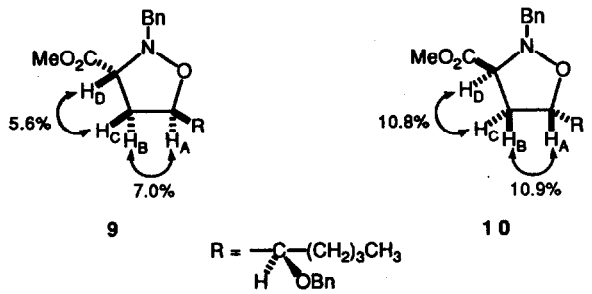
the isopropylidene group under acidic conditions and treatment of the 1,2-diol **5**, $[\alpha]^{20}_D$ +36.6° (c = 0.54, $CHCl_3$), with *N,N*-dimethylformamide dimethyl acetal afforded the 2-dimethylamino-1,3-dioxolane **6**, which was subsequently converted to the (*S*)-allyl ether **7**, $[\alpha]^{22}_D$ −39.8° (c = 0.65, $CHCl_3$), by heating with acetic anhydride in 68% overall yield from **4**.

The nitrone **8**, existing as an *E/Z* equilibrium mixture,[8] was allowed to react with **7** (toluene, reflux) to give a 3:1 mixture of the C-3, C-5-*trans* adducts **9** and **10** in 76% yield in favor of desired **9**.[9]

Scheme II



The trans stereochemistry of the products was confirmed by NOE measurements in their 400-MHz ^1H NMR spectra. NOE's of 7.0% and 5.6% were observed between H_A and H_B, and H_C and H_D, respectively, for **9**, and NOE's of 10.9% and 10.8% were observed between H_A and H_B, and H_C and H_D, respectively, for **10**; thus H_A and H_D proved to be trans oriented in both **9** and **10**.

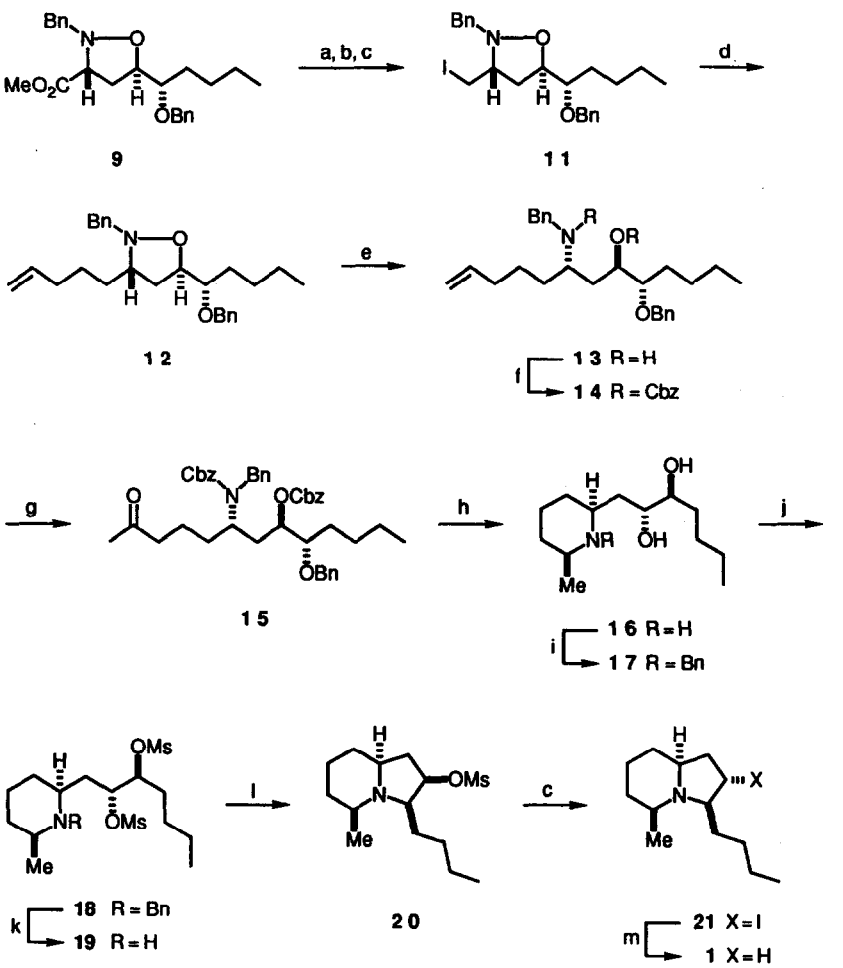


The trans stereochemical outcome observed in this cycloaddition is consistent with a reaction pathway involving exo addition of the *E* nitrone (*E*)-**8** (Scheme II). While considerable study has been made of asymmetric induction employing nitrone carrying chiral substituents on nitrogen or carbon, little exploratory work has been reported on asymmetric nitrone cycloaddition with chiral dipolarophiles.[10] Our present study, using a chiral allyl ether as a dipolarophile has thus proved to lead to asymmetric induction into a prochiral nitrone. The

formation of the major isomer **9** can be rationalized according to Houk's concept[11] by the preferred transition state conformation with the alkyl group anti to permit an antiperiplanar approach (Scheme II). When the alkoxy group (BnO) occupies an "inside" position σ^*_{C-O}/π overlap is minimized, and the transition state would be stabilized to lead to **9**. The alternative approach involving "outside" alkoxy conformation leading to **10** would be less favorable.

The major adduct **9** was converted to (+)-monomorine I [(+)-**1**] as outlined in Scheme III. Thus, **9** was transformed into the iodide **11**, $[\alpha]^{23}_D$ +37.2° (c = 1.60, $CHCl_3$), in 74% yield by sequential treatment with

Scheme III



(a) $LiAlH_4$, Et_2O; (b) TsCl, DMAP, $(i\text{-}Pr)_2NEt$, CH_2Cl_2; (c) NaI, MeCOEt, 75 °C; (d) $CH_2{=}CH(CH_2)_2MgBr$, (2-thienyl)Cu(CN)Li, THF, −78 °C → room temperature; (e) Zn, AcOH–H_2O–THF, 60 °C; (f) $PhCH_2OCOCl$ (3 equiv), aq. Na_2CO_3; (g) O_2, $PdCl_2$, $CuCl_2$, DMF–H_2O, 80 °C; (h) H_2, 10% Pd–C, MeOH, then H_2, 10% Pd–C, 10% HCl–MeOH; (i) $PhCH_2Br$, Na_2CO_3, DMF, 70 °C; (j) MsCl, Et_3N, CH_2Cl_2, −20 °C; (k) H_2, 10% Pd–C, MeOH–dioxane; (l) Et_3N, CH_2Cl_2, reflux; (m) H_2, 10% Pd–C, Et_3N, MeOH.

$LiAlH_4$, TsCl, and NaI. Coupling was effected by using higher-order mixed organocuprate[12] derived from 3-butenylmagnesium bromide and lithium 2-thienylcyanocuprate, leading to **12**, $[\alpha]^{23}_D$ +77.9° (c = 2.62, $CHCl_3$), in 86% yield. Reductive N–O bond cleavage (Zn, aqueous AcOH) followed by treatment of the resultant amino alcohol **13** with $PhCH_2OCOCl$ (3 equiv) gave **14**, $[\alpha]^{25}_D$ +24.4° (c = 1.26, $CHCl_3$), in 80% yield from **12**. After oxidation of **14** via the Wacker process (O_2, $PdCl_2$, $CuCl_2$), the resultant ketone **15** (91% yield) underwent simultaneously reductive cyclization and debenzylation to yield the *cis*-2,6-dialkylpiperidine **16** as a single stereoisomer, which was subsequently converted to **17** by selective N-benzylation ($PhCH_2Br$, Na_2CO_3, DMF) in 52% overall yield. The di-*O*-mesylate **18**, $[\alpha]^{25}_D$ +31.9° (c = 0.31, $CHCl_3$); mp 141–143 °C, prepared from **17** (76% yield), was hydrogenolyzed to give **19**, which was immediately cyclized by heating with triethylamine in dichloromethane to afford **20**, $[\alpha]^{25}_D$ −15.1° (c = 0.27, $CHCl_3$); mp 47–47.5 °C, as a single diastereomeric product (66% overall yield). Finally, **20** was converted to (+)-monomorine I [(+)-**1**], $[\alpha]^{24}_D$ +33.3° (c = 0.39, hexane), by means of nucleophilic displacement (NaI) followed by reductive deiodination (H_2, Pd–C, Et_3N, MeOH). The synthetic material was identical ($[\alpha]_D$, TLC, ^1H NMR, and ^{13}C NMR) with an authentic sample previously prepared in this laboratory.[5]

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