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A NOVEL SYNTHESIS OF (+)-AZIMIC ACID

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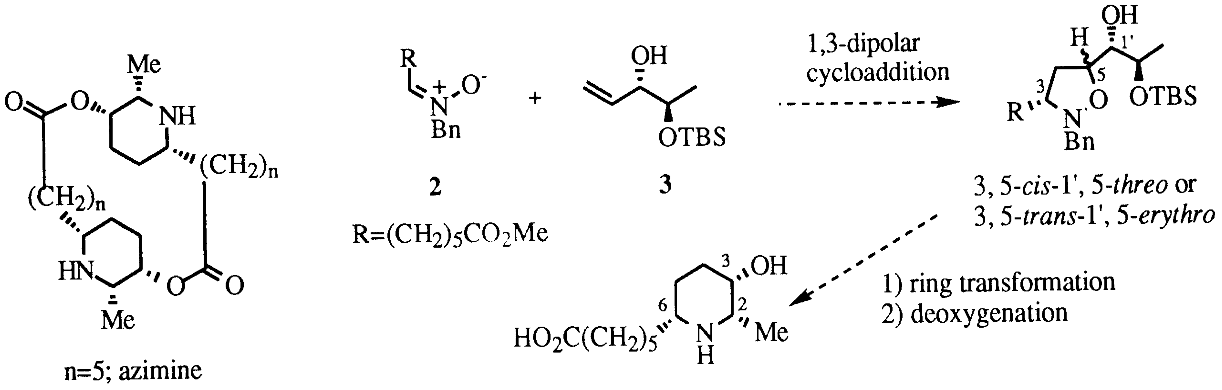
A combination of 1,3-dipolar cycloaddition of Z-nitrone (**2**) to the chiral dipolarophile (**3**) and subsequent ring transformation of the resulting adducts (**4** and **6**) to piperidinol (**17**) has provided a new practical synthesis of 2,3,6-trisubstituted piperidine alkaloid, (+)-azimic acid (**1**).

KEY WORDS azimine; azimic acid; 1,3-dipolar cycloaddition; nitrone; enantioselective synthesis; isoxazolidine

Piperidine alkaloids are abundant in nature and many of them exhibit important biological activity. Azimine and carpaine are two of the macrocyclic dilactones[1)] consisting of two molecules of characteristic 2,3,6-trisubstituted piperidines with carboxyl and hydroxyl groups, designated as azimic and carpamic acids. In addition, their interesting biological activities have attracted the interest of chemists as their synthetic targets as seen from several total synthetic studies.[2)]

Asymmetric cycloadditions of nitrones have been successfully applied to the synthesis of natural products by many groups.[3)] We now provide a potential method for synthesis of (+)-azimic acid (**1**) *via* the 1,3-dipolar cycloaddition of the nitrone (**2**) to the chiral dipolarophile (**3**) and the subsequent ring transformation of the resulting adducts to the piperidinols and their deoxygenation reaction.



n=5; azimine
n=7; carpaine

2
$R=(CH_2)_5CO_2Me$

3

(+)-azimic acid **1**

Our study[4)] on the 1,3-dipolar cycloaddition of *C,N*-dialkylnitrone to the allyl alcohols established that the reaction rate and the stereoselectivities are influenced by the form of the hydroxyl group, of which the rate was accelerated and the *trans*-selectivity was improved when the magnesium alkoxide (OMgBr)[5)] is used. For the synthesis of (+)-azimic acid (**1**), we first investigated the magnesium-induced cycloaddition of Z-nitrone (**2**),[6)] prepared from *N*-benzylhydroxylamine and methyl 7-oxoheptanoate,[7)] to the allyl alcohol (**3**) which was prepared from methyl (-)-lactate according to the known procedure.[8)] The allyl alcohol (**3**) was treated with methylmagnesium bromide and the resulting magnesium alkoxide with nitrone (**2**) in methylene dichloride under reflux to give a 1:4 mixture of two adducts (**4**) and (**5**) in 17% combined yield with recovery of a large amount of **3**. Thus, magnesium-induced cycloaddition of Z-nitrone (**2**) took place with *trans*-stereoselectivity to give a *trans-threo* isomer (**5**), which was not suited for the synthesis of (+)-azimic acid (**1**). On the other hand, cycloaddition of Z-nitrone (**2**) to the free allyl alcohol (**3**) in toluene under reflux proceeded smoothly to give a mixture of three adducts (**4**—**6**) in 83% combined yield which was readily separated by chromatography. Their stereochemistries were deduced from the structures of the

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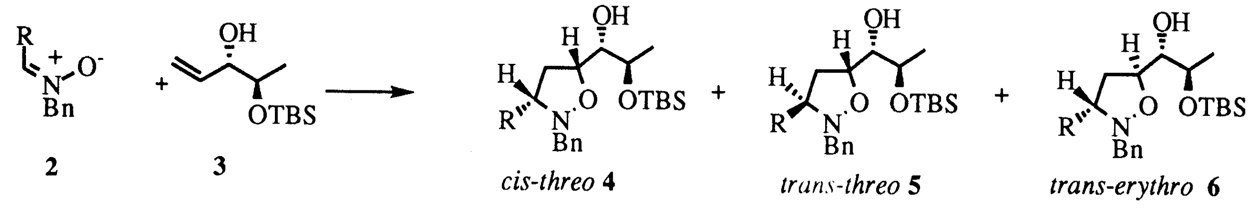
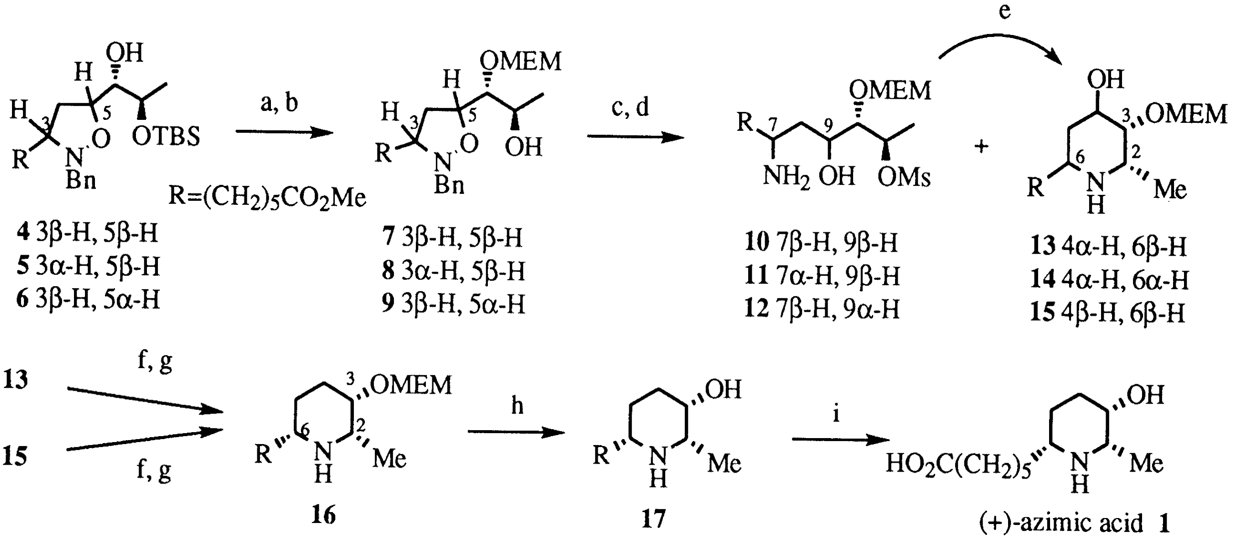
corresponding ring-transformed piperidinols as shown below. Of three adducts (**4**—**6**), the *cis-threo* (**4**) and *trans-erythro* (**6**) were employed for the synthesis of (+)-azimic acid (**1**). The *threo*-selectivity observed in both cycloadditions to magnesium alkoxide and to free alcohol was in accordance with the known results.[9)]



Condition	Additive	Yield (%) 4	Yield (%) 5	Yield (%) 6
CH_2Cl_2/Δ, 30h	MeMgBr	3	14	—
Toluene/Δ, 50h	-	35	37	11

threo > *erythro*

Protection of the hydroxyl group in the adducts (**4**—**6**) with MEM chloride and deprotection of the silyl group with TBAF gave the alcohols (**7**—**9**) in 54—76% yields. Upon treatment with methanesulfonyl chloride-pyridine, the alcohols (**7**—**9**) gave the corresponding mesylates which were then treated with hydrogen in the presence of Pearlman's catalyst to yield a mixture of the ring-transformed piperidinols (**13**—**15**) and the acyclic mesylates (**10**—**12**). For the completion of the cyclization reaction of the acyclic mesylates, the crude hydrogenated products were treated with $NaHCO_3$ in $MeOH-H_2O$ to give the piperidinols (**13**—**15**)[10)] in 62—93% yields *via* 3 steps which were characterized with the ^{1}H-NMR spectra. Deoxygenation of the piperidinols (**13**) and (**15**) *via* Barton's ester[11)] gave the identical piperidine (**16**) in 93% yield from **13** and 81% yield from **15**, respectively. Deprotection of the MEM group in **16** was achieved by treatment with $TiCl_4$ to give the piperidinol (**17**)[10)] in 81% yield. The hydrolysis of the ester group in **17** with KOH-MeOH gave (+)-azimic acid (**1**), which was found to be identical with the authentic sample of (+)-**1** upon comparisons of their spectral data[2ab)] including optical rotation [colorless crystals (MeOH), m.p. 217°C (dec.), $[\alpha]_D$ +7.4° (*c*=0.52, MeOH), lit. m.p. 210-214°C (dec.),[2c)] 214-215°C (EtOH),[2b)] $[\alpha]_D$ +7.9° (*c*=1, MeOH)[2b)]].



Reagent; (a) MEMCl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, Δ; (b) $(n\text{-}Bu)_4NF$, THF, Δ; (c) MsCl, Py., 0°C; (d) 20% $Pd(OH)_2$-C, MeOH, H_2; (e) $NaHCO_3$, H_2O-MeOH; (f) Im_2CS, THF; (g) Bu_3SnH, Toluene, Δ; (h) $TiCl_4$, CH_2Cl_2, 0°C;
(i) MeOH, HCl

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6) The Z configuration of nitrone (**2**) was firmly deduced by comparison of ^{1}H-NMR spectrum with those of the related nitrones.$^{4)}$ **2**: Colorless plates. m.p. 65-67°C (Et_2O). IR ($CHCl_3$) cm^{-1}: 1731 (CO_2), 1600 (C=N). ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 6.63 (1H, t, J=6 Hz, $HC=N^+$), 4.87 (2H, s, CH_2Ph). *Anal.* Calcd for $C_{16}H_{17}NO$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.15; H, 8.10; N, 5.16.

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10) **13**: Colorless oil. IR ($CHCl_3$) cm^{-1}: 3402 (OH), 1731 (CO_2). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.12 (1H, q, J=3 Hz, 4-H), 3.36 (1H, br t, J=2 Hz, 3-H), 3.27 (1H, br q, J=6 Hz, 2-H), 2.98 (1H, m, 6-H), 2.30 (2H, t, J=7 Hz, 5'-H_2), 1.67 (1H, br dt, J=14, 2.5 Hz, 5-Heq), 1.57 (1H, ddd, J=14, 11, 3 Hz, 5-Hax), 1.18 (3H, d, J=6.5 Hz, 2-Me). $[\alpha]_D$ -11° (c=1.43, MeOH). **14**: Colorless oil. IR ($CHCl_3$) cm^{-1}: 3441 (OH), 1731 (CO_2). ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.71 (1H, ddd, J=11, 8.5, 5 Hz, 4-H), 3.42-3.37 (2H, m, 2, 3-H), 2.82 (1H, m, 6-H), 2.27 (2H, t, J=7 Hz, 5'-H_2), 2.03 (1H, ddd, J=13, 5, 3 Hz, 5-Heq), 1.11 (3H, d, J=7 Hz, 2-Me) 1.06 (1H, br dt, J=13, 11.5 Hz, 5-Hax). $[\alpha]_D$ -46° (c=0.89, MeOH). **15**: Colorless oil. IR ($CHCl_3$) cm^{-1}: 3443 (OH), 1732 (CO_2); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.53 (1H, ddd, J=11, 5, 4 Hz, 4-H), 3.48 (1H, br s, $W_{1/2}$=5.5 Hz, 3-H), 2.73 (1H, qd, J=6.5, 1 Hz, 2-H), 2.54 (1H, m, 6-H), 2.30 (2H, t, J=7.5 Hz, 5'-H_2), 1.76 (1H, br dt, J=12, 3 Hz, 5-Heq), 1.23 (1H, br q, J=12 Hz, 5-Hax), 1.12 (3H, d, J=6.5 Hz, 2-Me). $[\alpha]_D$ +7° (c=1.02, MeOH). **17**: Colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.61 (1H, m, $W_{1/2}$=6.5 Hz, 3-H), 2.84 (1H, qd, J=6.5, 1.5 Hz, 2-H), 2.61 (1H, m, 6-H), 2.31 (2H, t, J=7 Hz, 5'-H_2), 1.94 (1H, br dq, J=10.5, 3 Hz, 4-Heq), 1.69—1.24 (11H, m, 4-Hax, 5-H_2, 1"—4"-H_2), 1.18 (3H, d, J=6.5 Hz, 2-Me).

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