A FACILE ALDOL-ISOMERIZATION ROUTE TO 3-ALKYLDIHYDROPYRIDINONE WITH A CHIRAL AZOCINE RING

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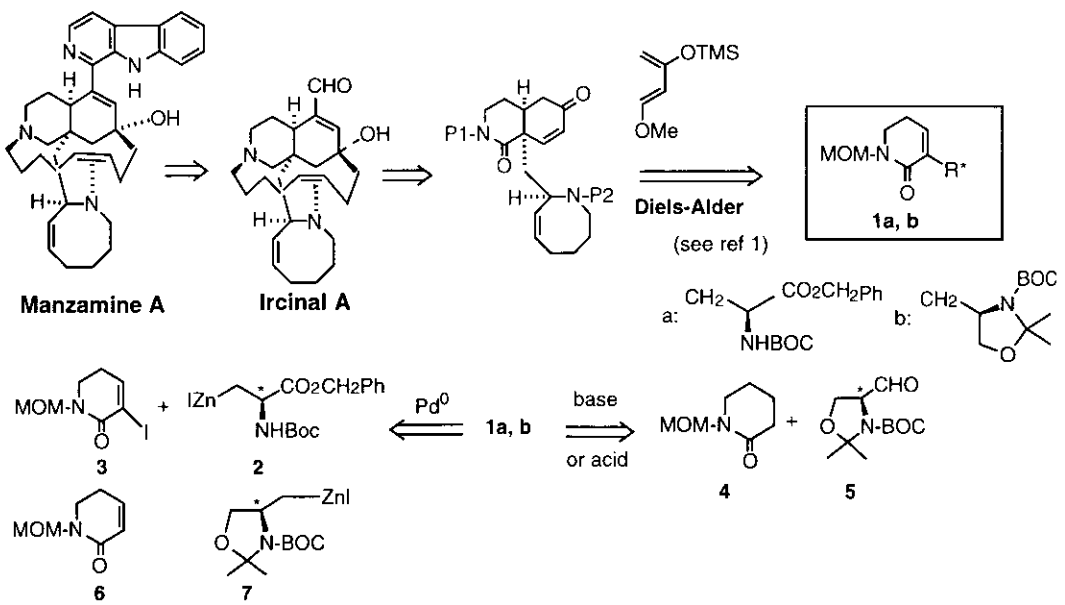
Abstract - *An efficient protocol was devised for the synthesis of the chiral dihydropyridinone derivative (**19**), which involves an aldol-type coupling reaction between N-alkylpiperidin-2-one and Garner aldehyde followed by a silane-Rh-mediated olefin isomerization.*

Pyridones and dihydropyridinones are versatile synthetic intermediates and important core structures in heterocyclic chemistry with biological relevance. In our synthetic approach to the marine alkaloid manzamine A, some dihydropyridinones have emerged as potential precursors for the construction of highly functionalized perhydroisoquinoline skeletons.[1] Although several interesting synthetic approaches to manzamine A have been developed,[2] few asymmetric strategies have been reported to date.[2d,e,m,o] Therefore, we felt that developing a general and efficient synthesis for dihydropyridinone derivatives bearing a chiral side chain, such as **1**, would significantly enhance the utility of our Diels-Alder methodol-

Scheme 1

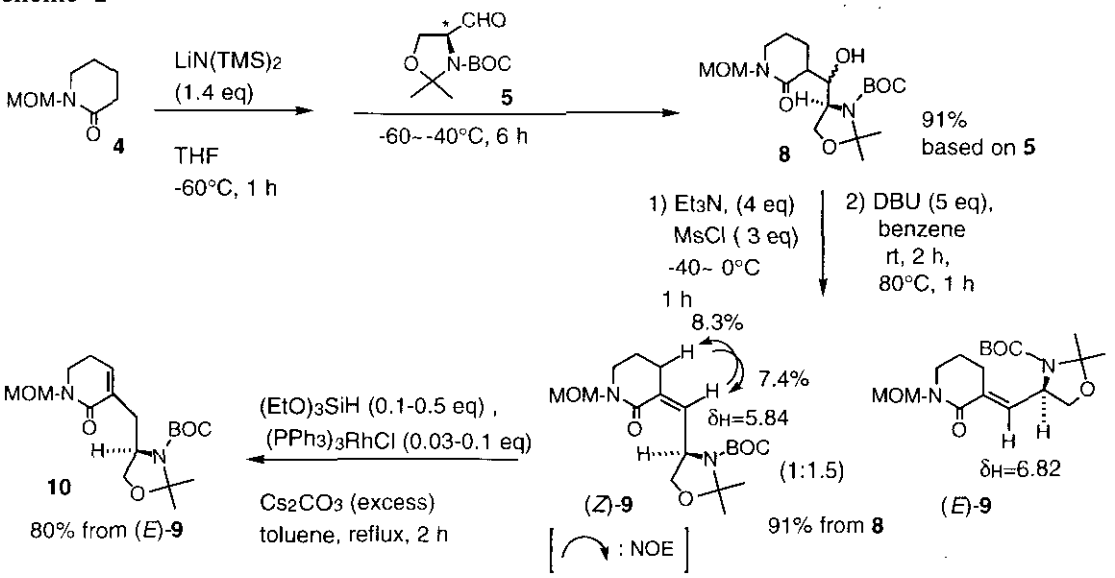


Dedicated to Prof. Koji Nakanishi on the occasion of his 75th birthday.

ogy.[1] Therefore, we decided to investigate the feasibility of a coupling reaction of vinyl iodide (**3**) with a chiral organozinc reagent, chiral amino acid unit (**2**), in the presence of Pd catalyst. The methodology originally reported by Jackson[3] and demonstrated by others in several recent applications[4] seemed attractive for our purpose. Another approach, an aldol-type coupling reaction between the enolate of *N*-alkylpiperidin-2-one (**4**) and Garner aldehyde (**5**)[5] was investigated as a more practical route to the chiral key intermediate for manzamine A. We present here synthetic routes leading to chiral dihydropyridinone derivatives (**1a**) and more advanced intermediate (**19**).

The approach outlined in Scheme 1 starts with the Pd-mediated coupling reaction of the chiral organozinc species (**2**)[3,4] with (**3**)[6] under various conditions.[7] Among the catalyst systems examined, $PdCl_2(PhCN)_2$ (0.2 eq) combined *in situ* with tri-*o*-tolylphosphine (0.4 eq) in DMF provided a suitable catalytic species.

Scheme 2



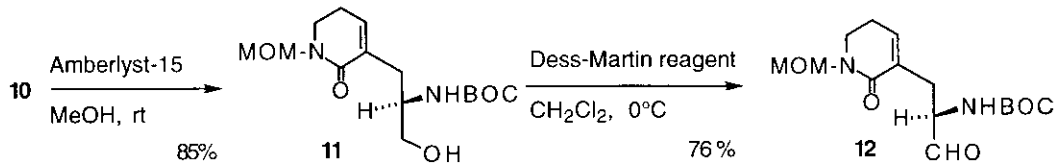
Under these conditions, dihydropyridinone (**1a**) was produced in the best yield (37%). A similar reaction of oxazolidine derivative (**7**) with **3** did not give **1.** Therefore, we searched for a further efficient route to obtain **1** which involves the aldol reaction of **4** with **5**.

The coupling reaction of the Garner aldehyde (**5**) with *N*-MOM-piperidone (**4**) under basic conditions [$LiN(TMS)_2$, THF, -60~-40°C] gave alcohols (**8**, mixture of diastereomers) in a yield of 80-90%, which were then dehydrated to give **9** under usual conditions. After purification, only *exo*-enones (**9**, *E* and *Z* mixture, 91%) were obtained. These were then subjected to *exo-endo* olefin isomerization to **10**. After some abortive experiments with conventional acid or base treatment [HCl, TsOH, PPTS, SiO_2, KOH, *t*-BuOK, DBU, $KN(TMS)_2$, LDA],[8] we found that $RhCl_3$-mediated isomerization[9] was promising, although it was very sluggish and gave a low yield ($RhCl_3.H_2O$, EtOH, reflux 3 days, 30%).

To circumvent this problem, a silane-Rh-mediated isomerization was examined closely. While a previously reported protocol [Et_3SiH, $RhCl(Ph_3P)_3$, toluene, reflux][10] gave more satisfactory results (~50% with 30% recovery of **9**), further optimization was needed. A high-yield isomerization reaction

was finally realized when the silane was changed to $(EtO)_3SiH$ and the reaction was conducted in the presence of Cs_2CO_3. In this way, the chiral dihydropyridinone derivative (**10**) was obtained in 80% yield from the major isomer [(*E*)-**9**][11] with a small amount of deprotected material. Although $RhCl_3$ olefin isomerization is a well-known process, only a few examples of successful conversion with nitrogen-containing systems have been reported.

Scheme 3

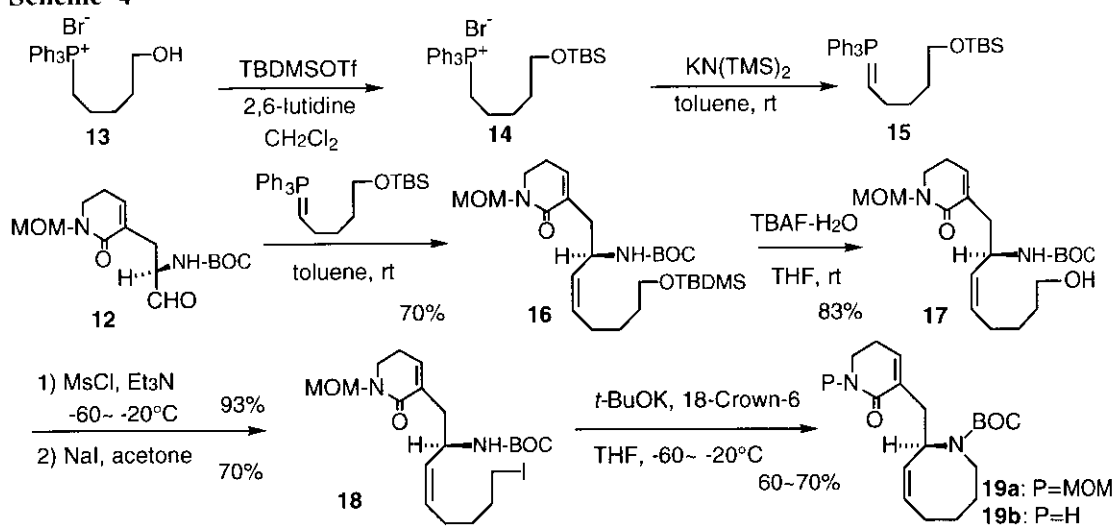


Compound (**10**) was deprotected to amino alcohol (**11**), which was then oxidized to the labile aldehyde (**12**) either by PCC-NaOAc-Al_2O_3 (75% after purification) or by Dess-Martin periodinane[12] (76%); the latter has proven to be a convenient and reliable reagent for this oxidation.

For elongation of the C5-carbon chain, Wittig reactions of conventional Wittig ylide derived from 4-carboxybutyltriphenylphosphonium bromide or 5-hydroxypentyltriphenylphosphonium bromide (**13**)[13] with **12** were carried out, but none of the desired products were obtained with these anionic oxido-ylides. However, Wittig reaction of **12** with the protected ylide (**15**) gave the desired product (**16**) in 70% yield, which was further transformed into the alcohol (**17**).[14]

The stage is now set for the crucial azocine ring-forming step. There are two options for the activation of the hydroxyl group towards azocine ring closure. Our previous protocol[1e] suggested the use of a tosylate rather than iodide for such cyclization. However, conversion of **16** to the *O*-monotosylate was simply accompanied by *N*,*O*-ditosylation, which did not lead to the desired cyclized product, but rather gave a simple elimination product.

Scheme 4



Alcohol (**17**) was then converted to iodide (**18**) *via* mesylation followed by treatment with NaI, and **18**

was cyclized in the presence of 18-crown-6 and *t*-BuOK to give the desired chiral azocine (**19a**)[15] in good yield (60-70%). Deprotection of the MOM group was effected under conventional conditions to furnish **19b** (TFA, CH_2Cl_2, 46%).

In summary, we have developed an efficient protocol for azocine containing a chiral intermediate for manzamine synthesis. Further transformation, including a key Diels-Alder reaction to the perhydroisoquinoline core of manzamine A, is now under active investigation in this laboratory.

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6. Compound (**3**) was prepared in 34% yield by the reaction of *N*-MOM-5,6-dihydropyridin-2-one (**6**) with NIS in CF_3CO_2H at rt for 1 h. All of the new compounds gave satisfactory spectral data and elemental analyses.

7. Our attempts to couple **3** with **2** which employed $(PhCN)_2PdCl_2$/P(o-tolyl)$_3$ by using coordinating solvents such as THF (6% yield of **1a**), DMA (33%), and THF-DMA (26%) did not give satisfactory results. Attempts to promote this coupling reaction by $Pd(OAc)_2$/$AsPh_3$/THF, $(Ph_3P)_4Pd$/THF, $(PdCN)_2PdCl_2$/(2MeOPh)$_3$P/THF-DMA, and $(PdCN)_2PdCl_2$/(4-MeOPh)$_3$P/THF-DMA were also unsuccessful.
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11. a) Isolated yields of two isomers of **9**: *E*-isomer, 55% ; *Z*-isomer, 36%. b) The yields of **10** by isomerization of **9**: 85% yield from *E*-isomer; 10% yield from *Z*-isomer. The structures of these two isomers were determined by ^{1}H-NMR and NOE.
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14. We have also succeeded in another Wittig olefination using the ylide derived from 4-cyanobutyltriphenylphosphonium bromide (50~60%). For the preparation and Wittig reaction of this ylide, see: 1g.
15. Selected spectral data for **19a**: $[\alpha]_D^{25}$ +23.0° (c=1.00, $CHCl_3$). IR (neat), cm^{-1}: 2925, 1680, 1660. MASS, LRFABMS, m/z: 365 (M^++H) 45%, 154 (100%). HRFABMS: Calcd for $C_{20}H_{33}N_2O_4$: 365.24419, Found: 365.2419. ^{1}H-NMR ($CDCl_3$), δ: 1.19-1.29 (2H, m, CH_2), 1.43 (9H, s, Boc), 1.60 (1H, m, CH_2), 1.76 (1H, br, CH_2), 1.99 (1H, br, CH_2), 2.25-2.34 (4H, m, $2CH_2$), 2.66 (1H, m, CH_2), 3.04 (1H, m, NCH_2), 3.29 (1H, s, NCH_2), 3.33 (3H, s, OMe), 3.45-3.49 (2H, m, NCH_2), 4.80 (1H, m, CH-N), 4.97 (2H, m, NCH_2O), 5.29 (1H, d like, J=11.4 Hz, CH=), 5.65 (1H, m, CH=), 6.32 (1H, br, CH=). ^{13}C-NMR ($CDCl_3$ at 50°C), δ: 24.21 (CH_2), 25.26 (CH_2), 25.72, 27.07 (Boc), 29.67 (CH_2), 34.88, 43.21 (NCH_2), 43.77 (CH), 54.47 , 55.96 (MeO), 76.69, 79.16 (Boc), 129.74, 131.19 (CH=), 132.50 (CH=), 137.11 (CH=), 155.66 (C=O), 165.66 (C=O).

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