Cross-Metathesis of Chiral *N*-*tert*-Butylsulfinyl Homoallylamines: Application to the Enantioselective Synthesis of Naturally Occurring 2,6-*cis*-Disubstituted Piperidines

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Received 18 July 2008

Abstract: The synthesis of piperidine alkaloids (+)-dihydropinidine (**1**), (+)-isosolenopsin (**2a**), (+)-isosolenopsin A (**2b**), and (2*R*,6*R*)-6-methylpipecolic acid (**3a**) hydrochlorides, based on cross-metathesis of chiral *N*-*tert*-butylsulfinyl homoallylamines with methyl vinyl ketone, is presented.

Key words: cross-metathesis, piperidine alkaloids, pipecolic acid derivatives, stereoselective allylation

Piperidine-containing alkaloids are commonly found in nature and exhibit a wide range of interesting biological activities.[1] These reasons have motivated considerable efforts on the enantioselective preparation of mainly 2,6-*cis*-disubstituted piperidines.[2] Among the numerous naturally occurring piperidines, simple 2-methyl-6-alkylpiperidines constitute an important class of alkaloids. Representative examples are dihydropinidine **1** (Figure 1), a defense alkaloid of the Mexican bean beetle *Epilachna varivestis*,[3,4] and isosolenopsins **2** (Figure 1),[5] venom alkaloids of fire ants. Structurally related *cis*-6-alkylpipecolic acids **3** (Figure 1), have also attracted the attention of synthetic chemists because they are key constituents of bioactive molecules and useful building blocks for asymmetric synthesis.[6]

An attractive strategy for the stereoselective synthesis of 2,6-*cis*-disubstituted piperidines is the reductive amination of δ-aminoketones. The usually excellent observed

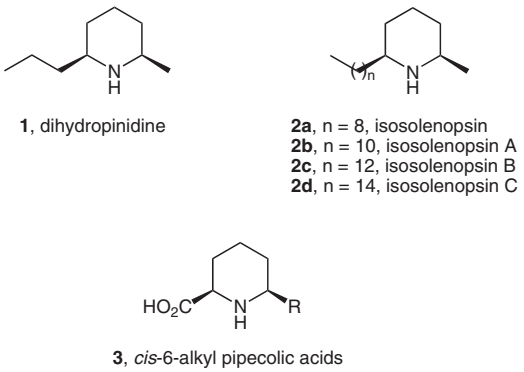
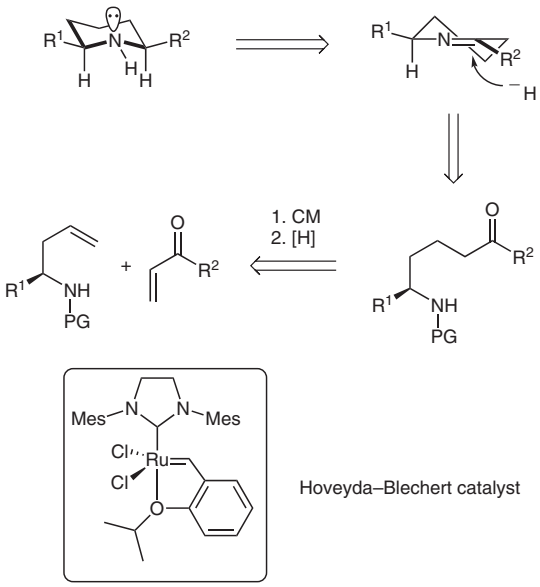


Figure 1

SYNLETT 2008, No. 18, pp 2777–2780
Advanced online publication: 15.10.2008
DOI: 10.1055/s-0028-1083535; Art ID: D27208ST

cis stereoselectivity is a consequence of the stereoelectronically preferred axial approach of the hydride to the most stable half-chair conformation of the iminium intermediate.[7] In this context, a novel sequence of cross-metathesis (CM) of chiral homoallyl amines and vinylalkylketones followed by reductive cyclization has been recently exploited in a number of enantioselective syntheses of 2,6-*cis*-disubstituted piperidine containing alkaloids.[8] A crucial finding for this approach was the Hoveyda–Blechert modification of the Grubbs II catalyst, which allows highly selective cross-coupling reactions between terminal alkyl-substituted and electron-deficient olefins (Scheme 1).[9]

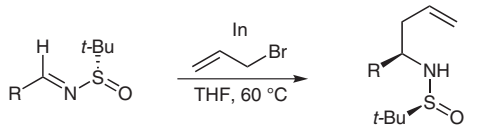


Scheme 1

In most of the reported enantioselective synthesis of *cis*-2,6-disubstituted piperidines using the CM-reductive amination sequence, chiral *N*-Cbz homoallyl amines were used to ensure hydrogenation of the double bond; N-deprotection and reductive amination were performed in the same synthetic operation. Due to its suitability for large-scale synthesis, the opening of chiral oxiranes by vinylmagnesium bromide followed by several functional group manipulations (usually six steps) has been the favorite approach to the necessary enantioenriched protected homoallylamines.[10] Since we have previously reported a simple

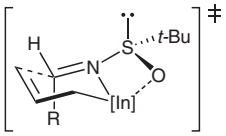
straightforward preparation of chiral *N-tert*-butylsulfinyl homoallyl amines,[11] we considered of interest to explore the use of these compounds in the CM-reductive amination sequence to obtain *cis*-2,6-disubstituted piperidines. To the best of our knowledge, there are few reports of ring-closing metathesis of dienes containing a *N*-sulfinyl moiety,[12] but no CM of *N*-sulfinyl homoallylamines, are reported in the literature. At the outset of this work it was unclear if the initial 'ruthenacycle' necessary for the metathesis would be poisoned by the *N*-sulfinyl moiety.

N-tert-Butylsulfinylamines[13] **5a–d** were conveniently prepared from the easily available (*S*)-*N-tert*-butylsulfinimines[14] **4a–d** by indium-mediated allylation under Barbier reaction conditions (Scheme 2).[15] Reactions were run on a 5-mmol scale in excellent yields and only one diastereoisomer was observed by ^{1}H NMR in all cases, except for compound **5a** where a 9:1 dr was observed. We assume that the allylation takes place at the *re*-face of the *S*-sulfinimine **4**, using a six-membered ring chelation control model, as previously proposed for this reaction. Since the newly created stereocenter would determine the absolute stereochemistry of the final known compounds, we decided to continue our synthesis hoping to confirm this information at the end of the process.



(+)-**4a**, R = *n*-Pr
(+)-**4b**, R = *n*-C_9H_{19}
(+)-**4c**, R = *n*-$C_{11}H_{23}$
(+)-**4d**, R = Ph

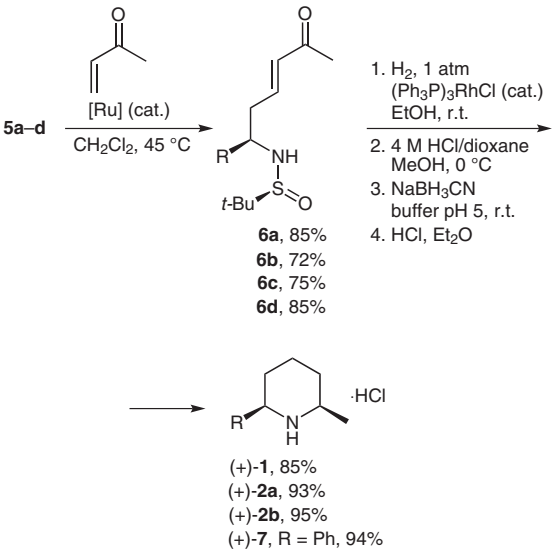
5a, 86%, dr 9:1
5b, 80%, dr >95:5
5c, 76%, dr >95:5
5d, 94%, dr >95:5



Scheme 2

We were pleased to observe that the CM of *N-tert*-butylsulfinylamines **5a–d** with commercially available methyl vinyl ketone took place smoothly when the Hoveyda–Blechert ruthenium catalyst [Ru] was used to afford exclusively the corresponding *E*-enones **6a–d** (Scheme 3). Importantly, 10 mol% of [Ru] catalyst and 48 hours were necessary to achieve good yields (72–85%),[16] probably due to the intramolecular chelation of the intermediate ruthenium species. Although similar results have been reported for *N*-Cbz homoallylamines, in our case it was not necessary to change the N-protecting group.

Although the sulfinyl group was proved to be tolerated under the CM conditions, all attempts to hydrogenate compound **6a** with Pd or Pt catalysts in different solvents were unsuccessful.[17] However, quantitative hydrogenation of the double bond of compounds **6a–d** was observed when the Wilkinson's catalyst was used. The

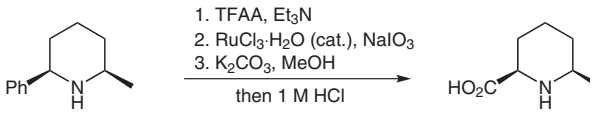


Scheme 3

sulfinyl group was removed using conventional acidic conditions to furnish the corresponding imine (GC–MS), which was reduced with $NaCNBH_3$ in a citrate–phosphate buffer medium (pH 5).[18] The expected piperidines were obtained in 85–95% yields over three steps and with a dr of 95:5 for aliphatic free piperidines **1**, **2a**, and **2b**, (GC–MS), whereas only one diastereoisomer was observed for **7** (Scheme 3). Hydrochlorides of compounds **1**, **2a**, and **2b** were crystallized using ethereal HCl and recrystallization from EtOH–EtOAc (1:3) afforded the corresponding pure products (>99:1, *cis*/*trans* ratio). Physical and spectroscopic data of hydrochlorides **1**, **2a**, and **2b** were in good agreement with those reported in literature. The good correlation of the specific rotation of our synthetic alkaloids **1**, **2a**, and **2b** with the data reported for the corresponding natural products show that no racemization occurred during the synthetic sequence and confirmed the absolute stereochemistry of *N-tert*-butylsulfinyl homoallylamines **5a–d**.[19]

2-Phenyl-6-methylpiperidine (**7**) was conveniently protected, and oxidation of the phenyl group in the presence of catalytic $RuCl_3$ and an excess of $NaIO_4$, followed by methanolysis of the trifluoroacetamide, afforded crude *cis*-6-methylpipecolic acid after acidification (Scheme 4).[20] The corresponding hydrochloride of the crude cyclic amino acid was purified using Dowex 50W-X8, followed by recrystallization from EtOH. The compound thus obtained showed $[\alpha]_D^{20}$ +10.5 (*c* 0.5, 0.1 M HCl) and spectral data in good agreement with the literature.[5a] Although the desired compound **3a** was isolated in only 41% yield, the clean ^{1}H and ^{13}C NMR spectra obtained just after elution through Dowex resin suggest that the loading of the amino acid onto the resin was not quantitative and that optimization in this isolation is possible. Most importantly, the specific rotation for the (2*R*,6*R*)-6-methylpipecolic acid (**3a**) suggests that no racemization has occurred during the synthetic sequence. With these results in hand, a general enantioselective synthesis of *cis*-

6-alkylpipecolic acids, compounds with interesting biological activities,[21] using compound **5d** and different vinyl alkyl ketones in the CM step can be readily envisaged.



7 (+)-**3a**, 41%

Scheme 4

In summary, we have reported here that enantioenriched *N-tert*-butylsulfinyl homoallylamines (easily prepared on the gram scale from inexpensive commercially available starting materials) underwent a smooth CM reaction with methyl vinyl ketone in the presence of the Hoveyda–Bletchert ruthenium catalyst. Hydrogenation of the enone intermediates in the presence of Wilkinson's catalyst, followed by reductive amination, allowed the efficient preparation of (+)-dihydropinidine (**1**), (+)-isosolenopsin (**2a**), and (+)-isosolenopsin A (**2b**) hydrochlorides. (2*R*,6*R*)-2-Phenyl-6-methylpiperidine (**7**) was also prepared using the same reaction sequence and was conveniently transformed into (2*R*,6*R*)-6-methylpipecolic acid (**3a**). Application of this approach to the synthesis of other natural alkaloids is currently under progress.

Acknowledgment

This work was generously supported by the Spanish Ministerio de Educación y Ciencia (MEC; Projects CTQ2007-65218/BQU and Consolider Ingenio 2010 CDS2007-00006). J.C.G.-G. thanks the Spanish MEC for a Juan de la Cierva contract.

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(16) **Preparation of Compound 6c**: A solution of amine **5c** (165 mg, 0.50 mmol), methyl vinyl ketone (140 mL, 1.65 mmol) and Hoveyda–Blechert ruthenium catalyst (31 mg, 0.05 mmol) in anhyd CH_2Cl_2 (10 mL) was stirred for 60 h at 45 °C. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, hexane–EtOAc) to give the title compound (137 mg, 0.37 mmol) as a pale brown oil; $[\alpha]_D^{28}$ +20.0 (*c* 0.32, $CHCl_3$). IR (neat): 3226, 1673, 1626 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 6.83 (dt, *J* = 16.0, 7.5 Hz, 1 H), 6.15 (d, *J* = 16.0 Hz, 1 H), 3.33–3.42 (m, 1 H), 3.09 (d, *J* = 7.7 Hz, 1 H), 2.51–2.56 (m, 2 H), 2.27 (s, 3 H), 1.22–1.55 (m, 20 H), 1.21 (s, 9 H), 0.88 (t, *J* = 7.6 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.3, 143.5 (CH), 133.9 (CH), 56.1, 56.0 (CH), 39.5 (CH_2), 35.7 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 29.25 (CH_2), 29.2 (CH_2), 27.0 (Me), 25.6 (CH_2), 22.55 (CH_2), 22.5 (Me), 14.0 (Me). LRMS (MALDI): *m/z* = 372.281 [M + H], 394.286 [M + Na].

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(18) **General Procedure for the Reductive Amination of Cross-Metathesis Products**: A flame-dried flask was cooled under a stream of argon and charged with

Wilkinson's catalyst (50 mg, 0.05 mmol) and a solution of the corresponding enone (1.10 mmol) in EtOH (5.0 mL). A balloon of H_2 was connected to the flask and the reaction mixture was stirred at r.t. overnight. After changing the solvent to *n*-hexane–*t*-BuOMe (1:1), the resulting suspension was filtered through a short pad of Celite to remove the solid Ph_3PO. The organic solution was concentrated (15 Torr) and the crude aminoketone was dissolved in MeOH (3 mL) and 4 M HCl in dioxane (1.5 mL) was added at 0 °C. After 1 h stirring at the same temperature, solvents were evaporated under vacuum. The residue was dissolved in citrate–phosphate buffer (1.5 mL) and THF (1.5 mL), adjusting the pH to 5 with 1 M NaOH if necessary. To this solution was added $NaCNBH_3$ (50 mg, 0.80 mmol) at 0 °C and the mixture was stirred for 3 h at 23 °C. The reaction mixture was basified with 15% NaOH (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with brine, dried over K_2CO_3 and concentrated (15 Torr) to afford the desired piperidines as pale yellow oils. The corresponding hydrochlorides were crystallized using ethereal HCl and recrystallization from EtOH–EtOAc (1:3) afforded pure products (*cis*/*trans* >99:1), having spectral data identical with those reported in literature.[4b]

(19) Specific rotations obtained for hydrochlorides **1**, **2a**, and **2b**:
(+)-Dihydropinidine hydrochloride: $[\alpha]_D^{20}$ +14.2 (*c* 0.66, EtOH) {Lit.[4a] $[\alpha]_D^{20}$ +14.1 (*c* 1.0, EtOH)}.
(+)-Isosolenopsin hydrochloride: $[\alpha]_D^{20}$ +10.2 (*c* 0.93, $CHCl_3$) {Lit.[4a] $[\alpha]_D^{20}$ +11.1 (*c* 0.92, $CHCl_3$)\.
(+)-Isosolenopsin A hydrochloride: $[\alpha]_D^{20}$ +11.0 (*c* 1.00, $CHCl_3$) {Lit.[4a] $[\alpha]_D^{20}$ +10.0 (*c* 1.17, $CHCl_3$)}.

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