Tetrahedron 68 (2012) 8863–8868

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of new 4-methyl-3-piperidones via an iron-catalyzed intramolecular tandem isomerization–aldolisation process

Dinh Hung Mac [a,c], Abdul Sattar [a,b], Srivari Chandrasekhar [b], Jhillu Singh Yadav [b], René Grée [a,*]

[a] Université de Rennes 1, Institut des Sciences Chimiques de Rennes CNRS UMR 6226, Avenue du Général Leclerc, 35042 Rennes Cedex, France
[b] Indian Institute of Chemical Technology, Division of Natural Products Chemistry, 500607 Hyderabad, India
[c] Hanoi University of Sciences, Medicinal Chemistry Laboratory, 19 Le Thanh Tong, Ha Noi, Viet Nam

ARTICLE INFO

Article history:
Received 17 June 2012
Received in revised form 13 August 2012
Accepted 16 August 2012
Available online 24 August 2012

Keywords:
Piperidines
Alkaloids
Azasugars
Iron pentacarbonyl
Catalysis
Tandem reactions

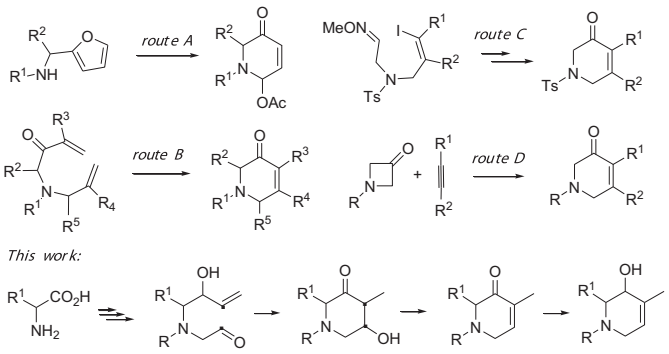
ABSTRACT

A new versatile synthesis of 3-piperidones is described, starting from amino acids. It uses, as a key step, an iron carbonyl-mediated intramolecular tandem isomerization–aldolisation reaction. These new heterocycles appear as useful scaffolds for the total synthesis of various types of bioactive molecules.

1. Introduction

Piperidine is a very important skeleton, both in the field of natural products and also for medicinal chemistry.[1] Piperidones are highly versatile intermediates toward such scaffolds. In particular, the 4-piperidones [2,3-dihydropyridin-4(1*H*)-ones] are readily accessible, either in racemic or optically pure form, and they have been much used in the literature[2] while, the corresponding [1,2-dihydropyridin-3(6*H*)-ones] have been less used, in spite of their excellent potential in synthesis. To the best of our knowledge, only four methods have been described to date for the preparation of such derivatives (Scheme 1). The first is the aza–Achmatowicz rearrangement (Route A), allowing preparation of 3-piperidones with an OAc or OR group in position 2.[3] The second is the ring closing metathesis (Route B), which has been especially developed for a versatile synthesis of 3-hydroxypyridines.[4] The third (Route C) is the intramolecular Heck-type reaction with oxime ethers, followed by a hydrolysis step.[5] The last method is a nickel-catalyzed [4+2] cycloaddition of 3-azetidinones with alkynes (Route D).[6] These methodologies allow elegant syntheses of various types of 3-piperidones and application of these intermediates to the synthesis of natural alkaloids, as well as in the preparation of 3-hydroxypyridines through elimination reactions. However, it is noteworthy that only two examples of optically active 3-piperidones have been reported to date: one by Route A, based on the use of chiral sulfinylimines (with 75% ee),[3] and another by Route D starting from a chiral azetidinone (up to 99% ee).[6]

Taking into account the excellent potential of such 3-piperidones in synthesis of alkaloids, as well as for azasugars, we became interested in designing a new versatile route to access these molecules.



Scheme 1. Various synthetic routes to 3-piperidones.

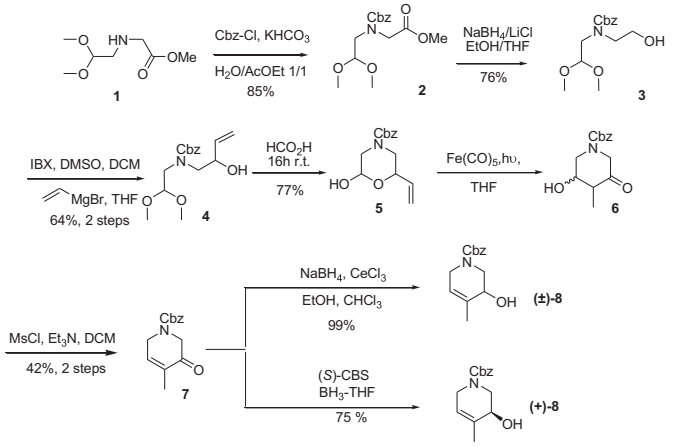
* Corresponding author. E-mail address: rene.gree@univ-rennes1.fr (R. Grée).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.08.048

Our strategy, based on the intramolecular tandem isomerization–aldolisation process developed in our group,[7] is indicated in Scheme 1: starting from amino acids it should be possible to prepare allylic alcohols with an aldehyde in remote position and connected through an amino linker. Then, if the tandem reaction is compatible with this nitrogen containing intermediate, the intramolecular process should lead to the aldol products and after dehydration to the targeted 3-piperidones. If desired, a final stereocontrolled reduction should give the corresponding 3-piperidols. One potential advantage of this new route is the easy access to a wide range of amino acids. On the other hand, both these new chiral 3-piperidones and corresponding 3-piperidols would be highly versatile intermediates for further synthetic applications. Therefore the purpose of this publication is to demonstrate, on three selected examples, the feasibility of this strategy.

2. Result and discussion

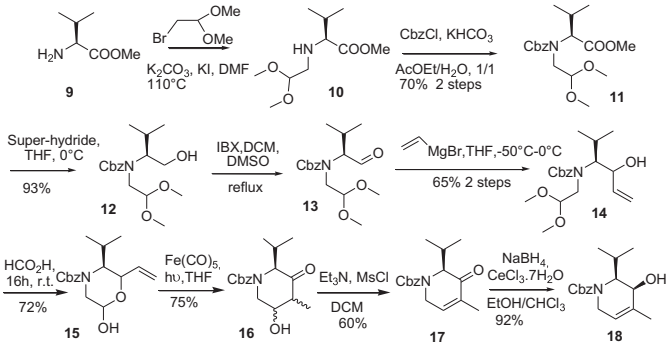
The 3-piperidone **7** and 3-piperidol **8** were selected as models to validate the synthetic strategy (Scheme 2). The known[8] aminoester **1** is easily accessible from 2,2-dimethoxyethylamine. Protection of **1** gave in good yield derivative **2**, which was reduced to aminoalcohol **3** in 76% yield.



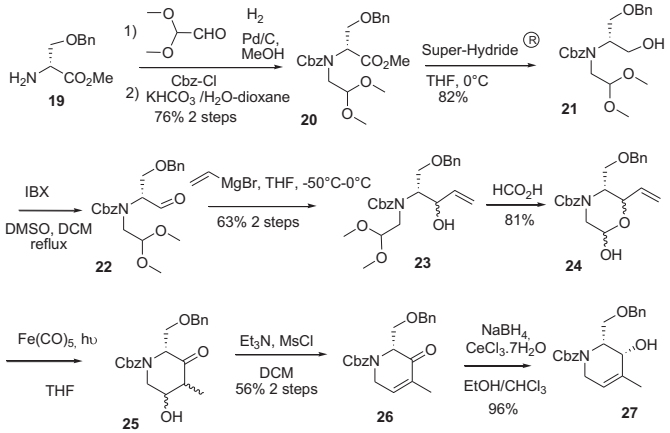
Scheme 2. Synthesis of 3-piperidone (±)-**7** and 3-piperidols (±)-**8**, (+)-**8**.

A 2-iodoxybenzoic acid (IBX)-mediated oxidation gave an aldehyde, which was reacted immediately with vinyl Grignard to give allylic alcohol **4** in 64% yield for the two steps. The acetal was removed using formic acid,[9] affording hydroxymorpholine **5** as a mixture of two stereoisomers, in 77% yield. In this molecule, only the closed form was observed by NMR without evidence for the corresponding hydroxy–aldehyde. Starting from this intermediate, the key tandem intramolecular isomerization–aldolisation process was successfully performed, by using $Fe(CO)_5$ as the catalyst at 10 mol %, affording aldol derivatives as a 60/40 mixture of diastereoisomers. These intermediates were reacted immediately with mesyl chloride and Et_3N to afford desired 3-piperidone **7** in 42% yield from **5**. Reduction with Luche's reagent[10] gave (±)-**8** in 99% yield, while asymmetric reduction using (*S*)-CBS agent gave allylic alcohol (+)-**8** in 75% yield. In agreement with literature data for similar type of molecules, (+)-**8** was obtained with a very high enantioselectivity (ee=99% by chiral HPLC analysis).[11] Therefore, through this synthesis, we have demonstrated that the tandem reaction was compatible with a Cbz-protected amino group. Further, the targets, 3-piperidone **7** and 3-piperidinol (+)-**8**, were obtained in 6 and 7 steps and 13% and 10% overall yields, respectively, from **1**.

The next step was to develop this strategy, starting from other amino acids. This has been done on two representative examples, one starting from L-Valine (Scheme 3) and the other one using D-Serine (Scheme 4) as starting material.



Scheme 3. Synthesis of 3-piperidone **17** and 3-piperidol **18**.



Scheme 4. Synthesis of 3-piperidone **26** and 3-piperidol **27**.

Starting from the methyl ester of L-Valine **9**, a two-step sequence alkylation with the bromoacetaldehyde dimethylacetal, followed by Cbz protection gave aminoester **11** in 70% yield. Then reduction to alcohol **12**, followed by IBX-mediated oxidation to **13** and vinyl Grignard addition, gave allylic alcohol **14** in 60% yield for the 3 steps.

Reaction with formic acid afforded, in 72% yield, hydroxymorpholine **15** ready for the key isomerization–aldolisation step. Under the same conditions as previously described, with $Fe(CO)_5$ as catalyst at 10 mol %, the reaction gave aldols **16**, as a mixture of stereoisomers, in 75% yield. They were immediately submitted to dehydration step to afford dihydropyridin3-one **17** in 60% yield. A final reduction, under Luche's conditions, was completely diastereocontrolled (^1H and ^{13}C NMR) with attack of hydride on the less hindered side opposite to bulky substituent, giving 3-piperidol **18** in 92% yield.

The next example was starting from the *O*-benzyl-protected methyl ester of L-Serine **19**. A reductive amination with monoprotected glyoxal, followed by Cbz protection gave intermediate **20** in 76% overall yield for the two steps. Then, the same sequence of reaction was followed to give the hydroxymorpholine **24** in 4 steps and 42% overall yield from **20**. The iron carbonyl-catalyzed tandem reaction was again successful and after dehydration, the target 3-piperidone **26** was obtained in 56% yield from **24**. Luche's

reduction afforded 3-piperidol **27**, with full diastereocontrol, in 96% yield.

3. Conclusion

In summary we have developed a new, flexible, route to 3-piperidones and corresponding 3-piperidols, starting from amino acids. This synthesis demonstrates that the tandem isomerization–aldolisation reaction is compatible with aza-derivatives, provided the nitrogen atom is suitably protected.[12] These new aza-heterocycles have useful functionalities, not only through the enone and allylic alcohol system, but also via the allylic methyl and methylene groups. Therefore they appear as versatile intermediates for the synthesis of various types of bioactive molecules, such as 4-alkyl analogs of fagomine or other azasugars, and corresponding results will be reported in due course.

4. Experimental section

4.1. General

All reactions were carried out under argon or nitrogen atmosphere. TLC spots were examined under UV light and revealed by sulfuric acid–anisaldehyde, $KMnO_4$ solution or phosphomolybdic acid. Dichloromethane was distilled from calcium hydride, tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone, methanol was distilled over magnesium. NMR spectra were obtained at 300 MHz or 500 MHz for ^1H and 75 MHz or 125 MHz for ^{13}C with BRUKER AVANCE 300 or 500 spectrometers. Chemical shifts are given in parts per million (δ) relative to chloroform (7.26 ppm) or benzene (7.16 ppm) residual peaks. Assignments of ^1H and ^{13}C resonances for complex structures were confirmed by extensive 2D experiments (COSY, HMQC, HMBC). Rotation data were recorded on a Perkin–Elmer 241 Polarimeter. Mass spectral analyzes have been performed with a Micromass ZaBSpecTOF at the Centre Régional de Mesures Physiques de l'Ouest (CRMPO) in Rennes (France).

Caution: all reactions involving $Fe(CO)_5$ have to be carried out under a well ventilated hood. These iron carbonyl-mediated reactions have been performed in usual Pyrex glassware equipment.

4.2. Preparation of 3-piperidones and 3-piperidols

*4.2.1. Methyl 2-((benzyloxycarbonyl)(2,2-dimethoxyethyl) amino) acetate (**2**).* To a solution of 2,2-dimethoxyethylamine (4 g, 38 mmol) in anhydrous diethyl ether (50 mL) was added slowly, dropwise, methyl bromoacetate (3.8 mL, 40 mmol) at 0 °C. The mixture was stirred at this temperature for another 30 min and then warmed up to rt. After 12 h, the formed solid was filtered, and the filtrate was washed by ether (100 mL), and then dried under vacuum. This salt was used for next step without further purification.

To a solution of previous hydrobromide (6.3 g) and $KHCO_3$ (10.9 g) in a mixture of ethyl acetate and water (50 mL/50 mL), was added CbzCl (3.7 mL, 23.6 mmol) at 0 °C. The reaction mixture was stirred at rt for 14 h and then hydrolyzed by a 10% HCl solution (50 mL). The organic phase was washed by a solution of brine (50 mL), dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude product was purified by column chromatography on silica gel (Eluent: Pentane/AcOEt 9/1) to give protected amine **2** as a colorless oil: 6.5 g, 55% overall yield from 2,2-dimethoxyethylamine.

^1H NMR (300 MHz, $CDCl_3$): δ=3.38 (s, 6H), 3.44 (dd, J=5.2, 9.5 Hz, 2H), 3.65 and 3.73 (s, 3H), 7.07 and 4.12 (s, 2H), 4.36 and 4.43 (t, J=5.1 Hz, 1H), 5.13 and 5.17 (s, 2H), 7.28–7.35 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=49.9, 50.0, 50.2, 50.6, 51.9, 52.0, 54.4, 54.6, 54.9, 66.9, 67.5, 67.7, 102.8, 103.9, 104.1, 127.8, 127.9, 128.1, 128.4, 128.5, 136.3, 136.4, 156.1, 156.2, 170.2. HRMS m/z calculated for $[M+Na]^+$ ($C_{15}H_{21}NO_6Na$): 334.1267, found 334.1270.

*4.2.2. Benzyl 2,2-dimethoxyethyl(2-hydroxyethyl)carbamate (**3**).* To a suspension of lithium chloride (1.79 g) in ethanol/THF (150 mL/100 mL) at 0 °C was added $NaBH_4$ (1.59 g), portionwise in 1 h. The mixture was stirred at rt for 1 h and then a solution of compound **2** (6 g, 19.3 mmol) in anhydrous THF (30 mL) was added. The reaction was stirred overnight at rt and then hydrolyzed by addition of water (50 mL). The aqueous phase was extracted by ethyl acetate (2×100 mL) and the combined organic phases were dried, filtered, concentrated under vacuum. The crude product was purified by column chromatography on silica gel (Eluent: Pentane/AcOEt 8/2, R_f=0.3) to give compound **3** as a colorless oil: 4.15 g, 76% yield.

^1H NMR (300 MHz, $CDCl_3$): δ=3.30 (s, 3H), 3.41 (s, 3H), 3.27–3.51 (m, 4H), 3.72 (broad s, 2H), 4.44 (t, J=5.2 Hz, 1H), 4.67 (t, J=5.3 Hz, 1H), 5.12 (s, 2H), 7.28–7.33 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=50.8, 51.8, 52.1, 52.5, 54.7, 56.0, 61.5, 61.7, 67.2, 67.5, 102.9, 103.7, 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, 136.2, 138.4, 155.4, 156.8. HRMS m/z calculated for $[M+Na]^+$ ($C_{14}H_{21}NO_5Na$): 306.1317, found 306.1312.

*4.2.3. Benzyl 2-hydroxy-6-vinylmorpholine-4-carboxylate (**5**).* To a suspension of IBX (3.95 g, 14 mmol) in a mixture of DMSO and CH_2Cl_2 (2 mL/20 mL) at 50 °C was added a solution of alcohol **3** (2 g, 7.07 mmol) in CH_2Cl_2 (10 mL). The reaction was stirred at this temperature for 24 h then hydrolyzed at rt by addition of water (5 mL). The suspension was filtered on Celite and the filtrate was washed with AcOEt (30 mL). The aqueous phase was extracted by AcOEt (2×30 mL). The combined organic phases were washed by water (3×50 mL) and a solution of brine (30 mL), dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude aldehyde (1.79 g) was used for the next step, without further purification.

To a solution of previous aldehyde in anhydrous THF (20 mL) was added dropwise vinyl magnesium bromide (10 mL, 1 M Solution in THF) at −50 °C. The reaction was stirred at this temperature during 2 h then warmed up to room temperature. After 1 h at rt, the reaction was hydrolyzed by addition of water (50 mL). The organic phase was extracted by AcOEt (2×50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was filtered through a short column on silica gel to give allylic alcohol intermediates **4** (1.38 g, 64% yield for 2 steps), which were used directly for next step, without further purification.

A solution of previous alcohols **4** in formic acid (15 mL of a commercial 88% solution) was stirred at rt for 16 h and then concentrated under vacuum. The residue was purified by column chromatography on silica gel (Eluent: Pentane/AcOEt 8/2; R_f=0.1) to afford lactols **5** (mixture of isomers) (916 mg, 49% overall yield for 3 steps) as a colorless oil.

^1H NMR (300 MHz, $CDCl_3$): δ=2.67–2.86 (m, 2H), 3.15 (d, J=13.5 Hz) and 3.29 (d, J=5.9 Hz, 1H), 4.02–4.24 (m, 2H), 4.61 (broad s, 1H) and 4.84 (broad s, 2H), 5.16 (s, 2H), 5.24 and 5.26 (dd, J=1.2, 10.7 Hz, 1H), 5.36 and 5.39 (dd, J=1.3, 17.3 Hz, 1H), 5.82 (ddd, J=5.5, 10.6, 16.5 Hz, 1H), 7.32–7.38 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=46.8, 48.3, 67.5, 68.1, 74.7, 92.6, 117.7, 117.9, 127.8, 128.0, 128.2, 128.5, 133.9, 137.7, 136.2, 155.1, 155.8. HRMS m/z calculated for $[M+Na]^+$ ($C_{14}H_{17}NO_4Na$): 286.1055, found 286.1052.

*4.2.4. Benzyl 4-methyl-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate (**7**).* A solution of lactols **5** (770 mg, 2.93 mmol) and $Fe(CO)_5$ (38 μL, 10% mol) in anhydrous THF (20 mL) was irradiated with a Philips HPK125 W until disappearance of starting material (TLC monitoring). After being cooled to rt and concentrated, the residue was diluted in ether, filtered on a short pad of silica gel, and

concentrated under vacuum to afford aldol products as a mixture of diastereoisomers. This mixture was purified by column chromatography on silica gel, with Pentane/AcOEt 7/3 as eluent, to afford the aldol adducts **6** (460 mg), used directly for next step.

To an ice-cold solution of previous aldols **6** (390 mg, 1.5 mmol) and Et_3N (630 μL, 5 equiv) in anhydrous CH_2Cl_2 (15 mL), was added MsCl (232 μL, 2 equiv) at 0 °C. After being stirred at rt for 24 h, the mixture was diluted with CH_2Cl_2 and H_2O. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under vacuum to afford a residue, which was purified by chromatography on silica gel, with Pentane/AcOEt (90/10; R_f=0.6) as eluent, affording piperidone **7** as a colorless oil, (301 mg, 42% overall yield for 2 steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ=1.84 (broad s, 3H), 4.19 (s, 2H), 4.27 (s, 2H), 5.17 (s, 2H), 6.78 (broad s, 1H), 7.32–7.40 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=15.1, 37.6, 43.2, 51.5, 67.7, 128.1, 128.3, 128.6, 140.6, 141.6, 155.8, 194.2. HRMS *m/z* calculated for $[M+Na]^+$ ($C_{14}H_{15}NO_3Na$): 268.0950, found 268.0948.

*4.2.5. Benzyl 5-hydroxy-4-methyl-5,6-dihydropyridine-1(2H)-carboxylate (**8**)*

*4.2.5.1. Synthesis of (±)-**8** by Luche reduction.* A suspension of enone **7** (60 mg, 0.245 mmol) and cerium chloride in a mixture of ethanol and chloroform (5 mL/3 mL) was stirred until complete dissolution of cerium chloride. The reaction was cooled down to −78 °C and then $NaBH_4$ was added in one portion to this solution. After completion of the reaction (TLC monitoring), the reaction was warmed up to rt, then hydrolyzed by addition of water (1 mL). The aqueous phase was extracted by CH_2Cl_2 (2×10 mL) then the combined organic phases were washed by a solution of brine, dried over $MgSO_4$, filtered, concentrated under vacuum. The residue was purified by flash chromatography (Eluent: pentane/AcOEt 90/10, R_f=0.5) to give desired allylic alcohol (±)-**8** as a colorless oil (60 mg, 99% yield).

*4.2.5.2. Synthesis of (+)-**8** by CBS reduction.* To a solution of (*S*)-CBS (1.25 mmol) in anhydrous THF (10 mL) was added dropwise, a solution of BH_3·THF (1.5 mmol) at 0 °C. The mixture was stirred at 0 °C for 30 min and then a solution of enone **7** (245 mg, 1 mmol) in anhydrous THF was added dropwise. Then the reaction mixture was stirred until complete consumption of starting material (TLC monitoring). The reaction was quenched by addition of anhydrous methanol (2 mL). The mixture was concentrated under vacuum and the crude product was purified by column chromatography on silica gel to give desired product (+)-**7** in 75% yield and 99% ee.

^{1}H NMR (300 MHz, $CDCl_3$): δ=1.82 (broad s, *J*=1.6 Hz, 3H), 3.42 (d, *J*=13.6 Hz, 1H), 3.69 and 3.75 (s, 1H), 3.93 and 3.88 (broad s, 2H), 4.12 and 4.18 (s, 1H), 5.16 (s, 2H), 5.49 (broad s, 1H), 7.33–7.38 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=20.1, 43.5, 48.0, 66.9, 67.3, 120.9, 127.9, 128.0, 128.5, 134.8, 136.6, 155.9. HRMS *m/z* calculated for $[M+Na]^+$ ($C_{14}H_{17}NO_3Na$): 270.1106, found 270.1103. Chiral HPLC analysis: column Chiracel ® OD 250*4.6; eluent hexane/EtOH 95:5 at 1.2 mL/min; UV detection at 225 nm (±)-**7** shows two peaks of equal intensity at 9.4 min and 15 min, while (+)-**7** shows peaks at 9.5 min (0.5%) and 15 min (99.5%). $[\alpha]_D^{20}$=+293 (*c*=0.116, MeOH).

*4.2.6. (S)-Methyl 2-((benzyloxycarbonyl)(2,2-dimethoxyethyl) amino)-3-methylbutanoate (**11**).* To a suspension of ester **9** (3.80 g, 22.7 mmol), K_2CO_3 (6.28 g, 45.7 mmol) and KI (4.5 g, 27.2 mmol) in anhydrous DMF solution (60 mL) was added 2-bromo-1,1-dimethoxyethane (3.12 mL, 25 mmol). The mixture was then heated at 110 °C for 24 h and then diluted with water (100 mL). The aqueous phase was extracted by ether (4×50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude product was used for the next steps, without further purification.

To the solution of this amine hydrobromide (4.8 g) and $KHCO_3$ (10.9 g) in a mixture of ethyl acetate and water (50 mL/50 mL) was added CbzCl (3.7 mL, 26.3 mmol) at 0 °C. The reaction was stirred at rt for 14 h and then washed by a 10% HCl solution (50 mL). The organic phase was washed by a solution of brine (50 mL), dried over $MgSO_4$, filtered, concentrated under vacuum. The residue was purified by column chromatography on silica gel (Eluent: Pentane/AcOEt 8/2 R_f=0.3) to give protected amine **11** as a colorless oil (5.6 g, 70% yield for 2 steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ=0.84 (broad s, 3H), 0.97 (d, *J*=5.9 Hz, 3H), 2.31 (broad s, 1H), 3.23 and 3.26 (s, 3H), 3.32–3.43 (5H), 3.57 (s) and 3.67 (s, 3H), 3.98 (d, *J*=10.2 Hz) and 4.17 (d, *J*=10.1 Hz, 1H), 4.42 and 4.58 (broad s, 1H), 5.16 (s, 2H), 7.28–7.33 (5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.9, 20.2, 20.6, 27.9, 28.4, 48.1, 49.3, 51.7, 54.4, 54.6, 54.8, 55.0, 65.6, 65.9, 67.4, 103.4, 103.8, 127.9, 128.4, 136.2, 156.2, 176.9. HRMS (ESI) Calculated for $[M+Na]^+$ ($C_{18}H_{27}NO_6Na$): 376.17361, found 376.1736.

*4.2.7. (S)-Benzyl 2,2-dimethoxyethyl(1-hydroxy-3-methylbutan-2-yl)carbamate (**12**).* To a solution of amine **11** (5 g, 14.2 mmol) in anhydrous THF (40 mL) was added at 0 °C a solution of Super-Hydride® (17 mL, 1 M solution in THF). The reaction was stirred at 0 °C for 90 min then warmed up to rt. The mixture was hydrolyzed by addition of water (50 mL) then extracted by AcOEt (3×30 mL). The combined organic phases were dried over $MgSO_4$, filtered, concentrated under vacuum. The residue was purified by column chromatography on silica gel (Eluent: Pentane/AcOEt 8/2, R_f=0.15) to give carbamate **12** as a colorless oil (4.24 g, 93%).

^{1}H NMR (300 MHz, $CDCl_3$): δ=0.77 (d, *J*=6.7 Hz) and 0.85 (d, *J*=6.7 Hz, 3H), 0.89 (d, *J*=6.7 Hz) and 0.97 (d, *J*=6.7 Hz, 3H), 1.64–176 (m, 1H), 1.90–2.04 (m, 1H), 3.29 (s) and 3.32 (s, 3H), 3.45 (s) and 3.49 (s, 3H), 3.41 (d, *J*=6.8 Hz, 1H), 3.41 (d, *J*=2.4 Hz, 1H), 3.65–3.79 (m, 4H), 4.54 (dd, *J*=3.8 Hz, 6.8 Hz), and 4.91 (dd, *J*=3.0 Hz, 7.9 Hz, 1H), 5.15–5.20 (m, 1H), 7.3–7.38 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=19.9. 20.3. 20.5. 27.1. 27.9. 54.8. 55.6. 55.7. 56.1. 61.7. 61.9. 67.3. 67.5. 102.9. 103.9. 127.8. 127.9. 128.2. 128.3. 128.5. 128.6. 136.4. 136.5. 156.9. 157.7. HRMS (ESI) Calculated for $[M+Na]^+$ ($C_{17}H_{27}NO_5Na$): 348.17869, found 348.1787.

*4.2.8. (S)-Benzyl 6-hydroxy-3-isopropyl-2-vinylmorpholine-4-carboxylate (**15**).* To a suspension of IBX (7.75 g, 27.6 mmol) in a mixture of DMSO and CH_2Cl_2 (2 mL/20 mL) at 50 °C was added a solution of alcohol **12** (3 g, 9.2 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at this temperature for 24 h then hydrolyzed at rt by addition of water (5 mL). The suspension was filtered on Celite, and then the filtrate was washed by AcOEt (30 mL). The aqueous phase was extracted by AcOEt (2×30 mL) and the combined organic phases were washed with water (3×50 mL), and a solution of brine (30 mL), dried over $MgSO_4$, filtered, concentrated under vacuum to give aldehyde **13**. This crude intermediate was used directly for next step without further purification.

To a solution of previous aldehyde **13** in anhydrous THF (20 mL) was added dropwise vinyl magnesium bromide (10 mL, 1 M solution in THF) at −50 °C. The reaction was stirred at this temperature for 2 h then warmed up to rt. After 1 h at rt, the reaction was hydrolyzed by addition of water (50 mL). The organic phase was extracted by AcOEt (2×50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was filtered through a short column on silica gel to give vinyl alcohols **14** (as a mixture of stereoisomers), which were used directly for next step without further purification.

A solution of previous alcohols **14** in formic acid (15 mL of a commercial 88% solution) was stirred at rt for 16 h and then concentrated under vacuum. The residue was purified by column

chromatography on silica gel (Eluent: Pentane/AcOEt 8/2; R_f=0.1) to afford lactols **15** (1.68 g, 47% for 3 steps) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ=0.84–1.05 (m, 6H), 2.16–2.27 (m, 1H), 2.70–2.83 (m, 1H), 3.09–3.20 (m, 1H), 3.56–4.26 (m, 3H), 4.49–4.81 (br, 1H), 5.10–5.40 (m, 4H), 5.89 (ddd, J=5.2, 10.7, 16.9 Hz, 1H), 7.35–7.57 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=19.6, 19.7. 19.8, 19.9, 22.3, 22.4, 22.5, 22.6, 25.4, 25.6, 25.7, 25.8, 43.6, 43.9, 45.2, 45.7, 58.3, 58.9, 59.6, 67.3, 67.5, 67.7, 70.3, 70.6, 77.8, 77.9, 88.2, 89.3, 89.6, 93.1, 93.2, 115.1, 115.3, 115.6, 115.8, 137.6, 127.9, 128.1, 128.2, 128.5, 128.6, 134.8, 134.9, 135.7, 135.9, 136.0, 136.3, 136.4, 155.7, 155.8, 156.4. HRMS (ESI) Calculated for $[M+Na]^+$ ($C_{17}H_{23}NO_4Na$): 328.1525, found 328.1525.

*4.2.9. (S)-Benzyl 5-hydroxy-2-isopropyl-4-methyl-3-oxopiperidine-1-carboxylate (**16**).* A solution of lactols **15** (720 mmg, 2.36 mmol) and $Fe(CO)_5$ (32 μL, 10% mol) in anhydrous THF (20 mL) was irradiated with a Philips HPK125 W until complete disappearance of starting material. After being cooled to rt and concentrated, the crude mixture was purified by column chromatography on silica gel (Eluent: Pentane/AcOEt 7/3) to afford aldol products as a mixture of stereoisomers (540 mg, 75%).

^{1}H NMR (300 MHz, $CDCl_3$): δ=0.87–1.09 (m, 6H), 1.15 (d, J=6.9 Hz, 3H), 1.20 (d, J=6.4 Hz, 1H), 2.13–2.22 (m, 1H), 2.36–2.51 (m, 1H) 2.67–2.75 (m, 1H) 3.02–3.59 (m, 1H), 4.09–4.51 (m, 1H), 5.02–5.21 (m, 1H), 7.36 (br, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=10.0, 10.1, 18.7, 19.0, 19.9, 20.3, 27.6, 29.0, 45.1, 45.3, 46.5, 47.3, 49.6, 50.0, 67.8, 67.9, 68.3, 68.9, 71.9, 72.5, 127.9, 128.3, 128.6, 135.8, 136.2, 155.7, 156.4, 205.8, 209.9. HRMS (ESI) Calculated for $[M+Na]^+$ ($C_{17}H_{23}NO_4Na$): 328.15248, found 328.1526.

*4.2.10. (S)-Benzyl 6-isopropyl-4-methyl-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate (**17**).* To an ice-cold solution of previous aldol products **16** (440 mg, 1.44 mmol) and Et_3N (980 μL, 7 equiv) in anhydrous CH_2Cl_2 (20 mL), was added MsCl (410 μL, 5.25 mmol) at 0 °C. After being stirred at rt during 24 h, the mixture was diluted with CH_2Cl_2 and H_2O. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under vacuum to afford a residue, which was purified by chromatography on silica gel with Pentane/AcOEt (90/10; R_f=0.6) as eluent to afford enone **17** as a colorless oil, (247 mg, 60% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ=0.80 (d, J=6.7 Hz), and 0.84 (d, J=6.7 Hz, 3H), 0.85 (d, J=6.7 Hz) and 0.89 (d, J=6.7 Hz, 3H), 1.74 (q, J=2.4 Hz), 1.78–1.91 (m, 1H), 3.70 (dd, J=2.2 Hz, 4.6 Hz) and 3.78 (dd, J=2.2 Hz, 4.6 Hz, 1H), 3.86 (dd, J=2.2 Hz, 4.6 Hz, 1H), 4.20 (d, J=9.6 Hz, 1H), 4.35 (d, J=9.6 Hz, 1H), 4.60 (dd, J=1.9 Hz, 4.8 Hz, 1H) and 4.67 (dd, J=1.9 Hz, 4.8 Hz, 1H), 5.0–5.14 (m, 2H), 6.47 (dq, J=1.9 Hz, 4.4 Hz) and 6.58 (dq, J=1.9 Hz, 4.4 Hz, 1H), 7.21–7.29 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=15.4, 15.5, 19.1, 20.0, 29.4, 29.7, 41.4, 41.7, 65.2, 66.0, 67.5, 67.6, 128.1, 128.2, 128.5, 128.6, 132.8, 133.1, 136.0, 136.3, 138.8, 139.6, 155.1, 155.5, 195.39, 195.44. HRMS (ESI) Calculated for $[M+Na]^+$ ($C_{17}H_{21}NO_3Na$): 310.1419, found 310.1422. $[\alpha]_D^{20}$=+61 (c=0.3, MeOH).

*4.2.11. (5S, 6S)-Benzyl 5-hydroxy-6-isopropyl-4-methyl-5,6-dihydropyridine-1(2H)-carboxylate (**18**).* A suspension of enone **17** (330 mg, 1.14 mmol) and cerium chloride (460 mg) in a mixture of ethanol and chloroform (14 mL/8 mL) was stirred until the complete dissolution of cerium chloride. The reaction was cooled down to −78 °C and then $NaBH_4$ (50 mg) was added in one portion to this solution. After completion of the reaction (TLC monitoring), the reaction was warmed up to rt then hydrolyzed by addition of water (1 mL). The aqueous phase was extracted by CH_2Cl_2 (2×10 mL) then the combined organic phases were washed by a solution of brine, dried over $MgSO_4$, filtered, concentrated under vacuum. The residue was purified by flash chromatography (Eluent: pentane/AcOEt 90/10 R_f=0.5) to give desired product **18** as a colorless oil (303 mg, 92% yield).

^{1}H NMR (300 MHz, $CDCl_3$): δ=0.89 (d, J=6.8 Hz, 3H), 0.90 (d, J=6.6 Hz, 3H), 1.82 (s, 3H), 2.19 (broad s, 1H), 3.7 (broad s, 1H), 4.04 (broad s, 2H), 4.43 (broad s, 1H), 5.10–5.19 (m, 2H), 5.36 (broad s, 1H), 7.29–7.37 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=18.6, 20.4, 21.4, 27.4, 43.0, 59.9, 67.2, 70.0, 118.4, 127.8, 127.9, 128.4, 136.6, 156.2. HRMS (ESI) Calculated for $[M+Na]^+$ ($C_{17}H_{23}NO_3Na$): 312.1576, found 310.1584. $[\alpha]_D^{20}$=−14.4 (c=0.36, MeOH).

*4.2.12. (R)-Methyl 3-(benzyloxy)-2-((benzyloxycarbonyl)(2,2-dimethoxyethyl)amino)-propanoate (**20**).* To a solution of amine **19** (2 g, 9.6 mmol) in MeOH (60 mL) was added sequentially a 60% aqueous solution of dimethoxyacetaldehyde (1 g, 9.6 mmol), and Pd/C (150 mg, 7.5%). The mixture was stirred at rt overnight under H_2 atmosphere. The suspension was filtered on Celite and the organic phase was evaporated under vacuum to give secondary amine (1.14 g, 5.5 mmol), which was used immediately for next step without further purification.

To the solution of previous amine (1.14 g, 5.5 mmol) in water/dioxane (10 mL/5 mL) was added $KHCO_3$ (0.92 g, 11.0 mmol) at rt. The mixture was cooled down to 0 °C by an ice-bath and then a solution of Cbz–Cl (12 mmol) in dioxane (15 mL) was added dropwise in 15 min. The reaction was warmed up to rt and stirred for another 2 h then EtOAc (40 mL) and water (20 mL) were added. The organic phase was washed by a 1 M HCl solution, dried over $MgSO_4$, filtered, evaporated under vacuum. The crude product was purified by column chromatography on silica gel (Eluent: EtOAc/Pentane 1/1; R_f=0.5) to give compound **20** as a colorless oil (3.14 g, 76% yield for 2 steps).

^{1}H NMR (300 MHz, $CDCl_3$): δ=3.28 and 3.33 (s, 3H), 3.40 (s, 3H), 3.45 (d, J=6.3 Hz, 1H), 3.53 and 3.73 (s, 3H), 3.62 (d, J=4.0 Hz, 1H), 3.68 (t, J=3.4 Hz, 1H), 3.83–4.05 (m, 2H), 5.02–5.23 (m, 2H), 7.29–7.39 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ=50.1, 50.6, 52.0, 52.2, 54.1, 54.5, 55.1, 55.2, 60.7, 61.1, 65.3, 67.5, 67.6, 68.3, 68.9, 73.1, 104.0, 104.3, 126.9, 127.6, 127.7, 127.8, 128.1, 128.4, 128.5, 128.6, 136.1, 136.4, 137.9, 138.0, 140.9, 155.8, 155.9, 169.9, 170.0. HRMS (ESI) Calculated for $[M+Na]^+$ ($C_{23}H_{29}NO_7Na$): 454.1842, found 454.1850.

*4.2.13. (S)-Benzyl 1-(benzyloxy)-3-hydroxypropan-2-yl(2,2-dimethoxyethyl)carbamate (**21**).* To a solution of ester **20** (3.1 g, 7.4 mmol) in anhydrous THF (50 mL) at 0 °C was added slowly a solution of Super-Hydride® (20 mL, 1 M in THF). The reaction was stirred at 0 °C for 90 min then warmed up to rt. The mixture was hydrolyzed by addition of water (50 mL) then extracted by AcOEt (3×30 mL). The combined organic phases were dried over $MgSO_4$, filtered, concentrated under vacuum. The residue was purified by column chromatography on silica gel (Eluent: Pentane/AcOEt 8/2; R_f=0.15) to give compound **21** as a colorless oil (2.44 g, 82%).

^{1}H NMR (300 MHz, $CDCl_3$) δ=3.07–3.14 (m, 1H), 3.20 and 3.23 (s, 3H), 3.28 (d, J=5.3 Hz, 1H), 3.36 (s, 3H) and 3.38 (s, 3H), 3.52–3.73 (m, 4H), 4.12 (m) and 4.28 (broad s, 1H), 4.34–4.37 (m, 2H), 4.71 (dd, J=3.2, 7.5 Hz, 1H), 5.00–5.13 (m, 2H), 7.14–7.28 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ=46.8, 48.1, 54.6, 55.2, 55.4, 55.9, 58.7, 60.1, 60.9, 61.9, 67.4, 67.5, 68.3, 68.5, 73.1, 77.2, 103.1, 103.8, 127.5, 127.56, 127.6, 127.7, 127.8, 128.0, 128.1, 128.2, 128.4, 128.5, 128.6, 136.3, 136.4, 137.9, 138.1, 156.7, 157.2. HRMS (ESI) Calculated for $[M+Na]^+$ ($C_{23}H_{29}NO_7Na$): 426.1893, found 426.1895.

*4.2.14. (R)-Benzyl 3-(benzyloxymethyl)-6-hydroxy-2-vinylmorpholine-4-carboxylate (**24**).* To a suspension of IBX (3.5 g, 12.5 mmol) in a mixture of DMSO and CH_2Cl_2 (2 mL/20 mL) at 50 °C was added a solution of alcohol **21** (2.4 g, 6.3 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at this temperature for 24 h then hydrolyzed at rt by addition of water (5 mL). The suspension was filtered on Celite, and the filtrate was washed by AcOEt (30 mL). The aqueous phase

was extracted by AcOEt (2×30 mL) and the combined organic phases were washed by water (3×50 mL), a solution of brine (30 mL), dried over $MgSO_4$, filtered, and concentrated under vacuum to give aldehyde **22**. This crude compound was used directly for next step, without further purification.

To a solution of previous aldehyde **22** (2.8 g) in anhydrous THF solution (20 mL) was added dropwise vinyl magnesium bromide (10 mL, 1 M solution in THF) at −50 °C. The reaction was stirred at this temperature for 2 h and then warmed up to rt. After 1 h at rt the reaction was hydrolyzed by addition of water (50 mL). The organic phase was extracted by AcOEt (2×50 mL). The combined organic phases were dried over $MgSO_4$, filtered, and evaporated under vacuum. The residue was filtered through a short column on silica gel to give allylic alcohols **23**, which were used directly for next step without further purification.

A solution of previous alcohols in formic acid (15 mL of a commercial 88% solution) was stirred at rt for 16 h then concentrated under vacuum. The residue was purified by column chromatography on silica gel (Eluent: Pentane/AcOEt 8/2; R_f=0.1) to afford lactols **24** (1.3 g, 51% overall yield for 3 steps, two stereoisomers in a 55:45 ratio) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ=2.65 and 2.72 (dd, J=9.3, 13.3 Hz, 1H), 2.91 (broad s, J=7.3 Hz, 1H), 3.07 (dd, J=2.2, 14.3 Hz, 1H), 3.44–3.57 (m, 1H), 3.59–3.74 (m, 1H), 3.87–4.55 (m, 5H), 4.73–4.81 (m, 1H), 5.05–5.53 (m, 5H), 5.69 (ddd, J=6.4, 10.3, 17.1 Hz, 1H), 7.14–7.28 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ=42.3, 42.7, 44.0, 44.6, 52.0, 52.2, 53.1, 53.4, 55.7, 63.9, 64.6, 64.5, 64.6, 67.3, 67.4, 68.5, 68.8, 69.4, 72.8, 72.9, 73.3, 75.7, 75.9, 77.2, 89.4, 89.8, 90.1, 93.2, 116.6, 116.8, 119.7, 127.3, 127.9, 128.0, 128.1, 128.3, 128.4, 128.5, 133.1, 133.8, 134.9, 136.4, 138.0, 138.2, 155.5, 155.9, 156.2. HRMS (ESI) Calculated for $[M+Na]^+$ ($C_{22}H_{25}NO_5Na$): 406.1630, found 406.1630.

*4.2.15. (R)-Benzyl 6-(benzyloxymethyl)-4-methyl-5-oxo-5,6-dihydropyridine-1(2H)-carboxylate (**26**).* A solution of lactols **24** (900 mmg, 2.35 mmol) and $Fe(CO)_5$ (32 μL, 10 mol %) in anhydrous THF (20 mL) was irradiated with a Philips HPK125 W until disappearance of starting material (TLC monitoring). After being cooled to rt and concentrated, the residue was diluted in ether, filtered on a short pad of silica gel, and concentrated under vacuum to afford crude aldol products. This mixture was purified by column chromatography on silica gel with Pentane/AcOEt 7/3 as eluent to afford aldols **25** (747 mg, 83%) as a mixture of stereoisomers used directly for the next step.

To an ice-cold solution of previous aldol products (540 mg, 1.4 mmol) and Et_3N (980 μL, 7 equiv) in anhydrous CH_2Cl_2 (20 mL), was added MsCl (410 μL, 5.25 mmol) at 0 °C. After being stirred at rt during 24 h, the mixture was diluted with CH_2Cl_2 and H_2O. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under vacuum to afford a residue, which was purified by chromatography on silica gel (Eluent: Pentane/AcOEt 90/10; R_f=0.6) to afford enone **26** as a colorless oil, (415 mg, 67%).

^{1}H NMR (300 MHz, $CDCl_3$) δ=1.78 (s, 3H), 3.58–3.79 (m, 2H), 3.95–4.09 (m, 1H), 4.34–4.61 (m, 3H), 4.71–4.79 (m, 1H), 5.07 and 5.09 (broad s, 2H), 6.59 and 6.69 (broad s, 1H), 7.11–7.28 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ=15.3, 42.7, 43.0, 60.3, 60.7, 67.6, 71.2, 71.3, 127.2, 127.6, 128.1, 128.2, 128.4, 128.6, 133.6, 1361, 137.8, 140.9, 141.0, 141.9, 155.1, 194.4. HRMS (ESI) Calculated for $[M+Na]^+$ ($C_{22}H_{23}NO_4Na$): 388.1525, found 388.1523. $[\alpha]_D^{20}$=−647.2 (c=0.18, MeOH).

*4.2.16. (5R, 6R)-Benzyl 6-(benzyloxymethyl)-5-hydroxy-4-methyl-5,6-dihydropyridine-1(2H)-carboxylate (**27**).* A suspension of compound **26** (160 mg, 0.44 mmol) and cerium chloride (180 mg, 0.48 mmol) in a mixture of ethanol and chloroform (3 mL/2 mL) was stirred until the complete dissolution of cerium chloride. The reaction was cooled down to −78 °C, then $NaBH_4$ (40 mg) was added in one portion to this solution. After completion of the reaction (TLC monitoring), the reaction mixture was warmed up to rt and then hydrolyzed by addition of water (1 mL). The aqueous phase was extracted by CH_2Cl_2 (2×10 mL) then the combined organic phases were washed by a solution of brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel (Eluent: Pentane/AcOEt 90/10, R_f=0.5) to give desired allylic alcohol **27** as a colorless oil (155 mg, 96%).

^{1}H NMR (300 MHz, $CDCl_3$) δ=1.80 (m, 3H), 3.48–3.62 (m, 2H), 3.83 (dd, J=9.7, 9.7 Hz, 1H), 4.1 (broad s, 1H), 4.43–4.58 (m, 3H), 4.88 (broad s, 1H), 5.15 (broad s, 2H), 5.35 (broad s, 1H), 7.27–7.37 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$) δ=18.2, 41.0, 66.9, 67.2, 68.6, 73.1, 117.8, 127.5, 127.6, 127.8, 127.9, 128.3, 128.4, 136.5, 137.7, 155.5. HRMS (ESI) Calculated for $[M+Na]^+$ ($C_{22}H_{25}NO_4Na$): 390.1681, found 390.1675. $[\alpha]_D^{20}$=+98.5 (c=0.2, MeOH).

Acknowledgements

This research has been performed as part of the Indo–French '*Joint Laboratory for Sustainable Chemistry at Interfaces*'. We thank CNRS, MESR, French Ministry for Foreign Affairs and CSIR for support of this research. We thank A. Valleix for the chiral HPLC analysis of compounds **7**. We thank Drs. P. Uriac, N. Gouault and Mrs. D. Grée for fruitful discussions. We thank CRMPO (Rennes) for the mass spectral studies. D.H.M. thanks Vietnam Nation Foundation for Science and Technology Development (NAFOSTED) for grant number 104.01-2011.52.

References and notes

1. For representative reviews see: (a) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139–165; (b) Chemler, S. *Curr. Bioact. Compd.* **2009**, *5*, 2–19; (c) Bates, R. W.; Sa-Ei, K. *Tetrahedron* **2002**, *58*, 5957–5978; (d) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953–2989; (e) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693–3712; (f) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729 and references cited therein.
2. For representative examples see: (a) Comins, D. L.; Joseph, S. P. *Adv. Nitrogen Heterocycl.* **1996**, *2*, 251–294; (b) Joseph, S.; Comins, D. L. *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 870–880; (c) Seki, H.; Georg, G. I. *J. Am. Chem. Soc.* **2010**, *132*, 15512–15513; (d) Gouault, N.; Le Roch, M.; Cheignon, A.; Uriac, P. *Org. Lett.* **2011**, *13*, 4371–4373 and references cited therein.
3. Leverett, C. A.; Cassidy, M. P.; Padwa, A. *J. Org. Chem.* **2006**, *71*, 8591–8601.
4. (a) Donohoe, T. J.; Fishlock, L. P.; Basutto, J. A.; Bower, J. F.; Procopiou, P. A.; Thompson, A. L. *Chem. Commun.* **2009**, 3008–3010; (b) Yoshida, K.; Kawagoe, F.; Hayashi, K.; Horiushi, S.; Imamoto, T.; Yanagisawa. *Org. Lett.* **2009**, *11*, 515–518.
5. Liu, H.; Wang, L.; Tong, X. *Chem. Commun.* **2011**, 12206–12208.
6. (a) Kumar, P.; Louie, J. *Org. Lett.* **2012**, *14*, 2026–2029; (b) During revision of our manuscript, another synthesis of enantiopure 3-piperidones starting from azetidin-3-ones has been published: Ishida, N.; Yukhi, T.; Murakami, M. *Org. Lett.* **2012**, *14*, 3898–3901.
7. (a) Petrignet, J.; Prathap, I.; Chandrasekhar, S.; Yadav, J. S.; Grée, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 6297–6300; (b) Petrignet, J.; Roisnel, T.; Grée, R. *Chem.—Eur. J.* **2007**, *13*, 7374–7384; (c) Mac, D. H.; Roisnel, T.; Branchadell, V.; Grée, R. *Synlett* **2009**, 1969–1973; (d) Mac, D. H.; Samineni, R.; Petrignet, J.; Srihari, P.; Chandrasekhar, S.; Yadav, J. S.; Grée, R. *Chem. Commun.* **2009**, 4717–4719; (e) Mac, D. H.; Samineni, R.; Sattar, A.; Chandrasekhar, S.; Yadav, J. S.; Grée, R. *Tetrahedron* **2011**, *67*, 9305–9310.
8. Hickmann, D. T.; Sreenivasachary, N.; Lehn, J. M. *Helv. Chim. Acta* **2008**, *91*, 1–15.
9. Gorgues, A. *Bull. Soc. Chim. Fr.* **1974**, 529–530.
10. Gemal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.
11. Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012 and references cited therein.
12. For examples of tandem isomerization–Mannich reactions, starting from allylic alcohols and using suitably protected imines, see: (a) Cao, H. T.; Roisnel, T.; Grée, R. *Lett. Org. Chem.* **2009**, *6*, 507–510; (b) Cao, H. T.; Roisnel, T.; Valleix, A.; Grée, R. *Eur. J. Org. Chem.* **2011**, *19*, 3430–3436; (c) Cao, H. T.; Grée, D.; Grée, R. *Synthesis* **2011**, *20*, 3297–3300; (d) Cao, H. T.; Roisnel, T.; Grée, R. *Eur. J. Org. Chem.* **2011**, *32*, 6405–6408; (e) Wang, M.; Xiang, X.-F.; Li, C.-J. *Eur. J. Org. Chem.* **2003**, *5*, 998–1003.