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TETRAHEDRON: *ASYMMETRY*

Enantioselective synthesis of the quinolizidine alkaloids (+)-myrtine and (−)-epimyrtine

Daniel Gardette, Yvonne Gelas-Mialhe,* Jean-Claude Gramain, Bertrand Perrin and Roland Remuson

Laboratoire de Chimie des Substances Naturelles, UMR 6504, Université Blaise Pascal (Clermont-Ferrand), 63177 Aubière Cedex, France

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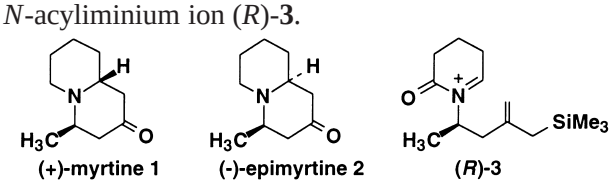
Abstract

The enantioselective synthesis of (+)-myrtine **1** and (−)-epimyrtine **2** is described starting from (*S*)-2-(2-hydroxypropyl)allyltrimethylsilane **4** using an intramolecular allylsilane *N*-acyliminium ion cyclization. © 1998 Elsevier Science Ltd. All rights reserved.

1. Introduction

(+)-Myrtine and (−)-epimyrtine are quinolizidine alkaloids isolated from *Vaccinium myrtillus* (Ericaceae).[1–3] Several total syntheses of these compounds as racemates have been described.[1–14] Only two enantioselective syntheses of (+)-myrtine have been published;[3,10] (−)-epimyrtine has never been synthesized.

We have shown that intramolecular cyclization of acyliminium ions substituted by an allylsilyl side chain as an internal π-nucleophile provided an efficient route to nitrogen bicyclic ring systems[15] and we have used this strategy to prepare a variety of alkaloids including (±)-myrtine **1** and (±)-epimyrtine **2**, *via* the cyclization of *N*-acyliminium ion **3**.[11] In this paper we report the enantioselective synthesis of these two alkaloids from *N*-acyliminium ion (*R*)-**3**.



* Corresponding author. E-mail: gelas@chisg1.univ-bpclermont.fr

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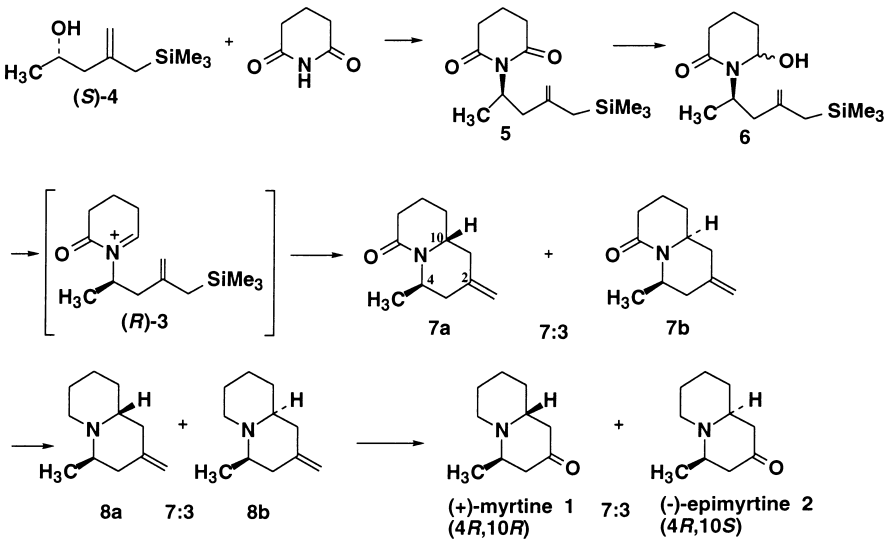
2. Synthesis of (+)-myrtine and (−)-epimyrtine

The reactions are depicted in Scheme 1. The starting material was (*S*)-2-(2-hydroxypropyl)allyltrimethylsilane **4** which was prepared in quantitative yield by cerium mediated trimethylsilylmethylmagnesium chloride addition to ethyl (*S*)-3-hydroxybutanoate, as we described recently.[16] The first three steps of the enantioselective synthesis were those previously described for the synthesis of the racemic compounds.[11] Condensation of alcohol **4** with glutarimide under Mitsunobu conditions led to (+)-imide **5** in 67% yield. The enantiopurity of this imide was determined based on the lanthanide-induced shift method. The ^{1}H NMR spectrum of the racemic mixture in the presence of 0.026 molar equivalent of tris(3-((trifluoromethyl)hydroxymethylene)-(+)-camphorato)europium(III), (Eu(tfc)$_3$), showed two well-resolved doublets for the methyl group at δ=1.49 and 1.50 ppm. (+)-Imide **5** with 0.023 molar equivalents of Eu(tfc)$_3$ showed a single doublet for these protons. Thus we established for imide **5** an enantiomeric purity of at least 95%.



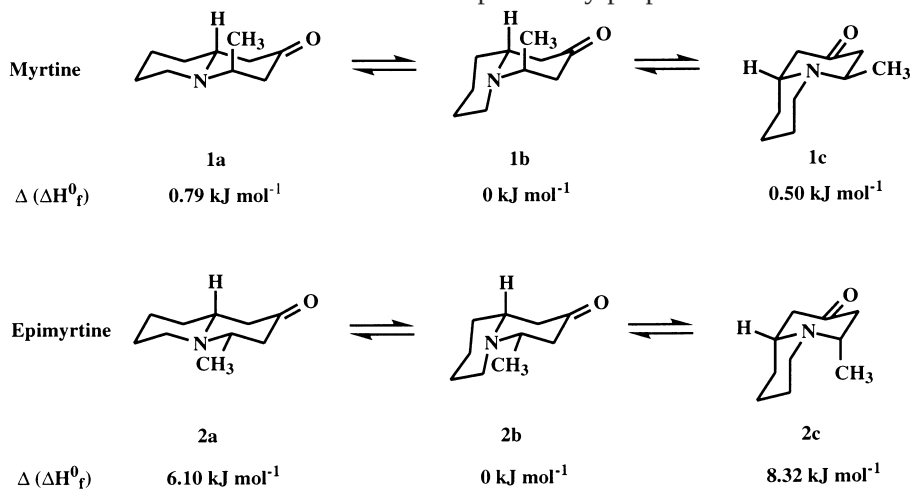
Scheme 1.

The Mitsunobu reaction is known to proceed in a stereospecific manner with inversion of configuration.[17] We concluded that (+)-imide **5** was the (*R*)-enantiomer. Reduction of **5** with sodium borohydride afforded hydroxylactam **6** as a 1:1 mixture of isomers in 95% yield. Treatment of hydroxylactam **6** with trifluoroacetic acid in methylene chloride gave a 7:3 mixture of the two isomeric bicyclic compounds **7a** and **7b** in quantitative yield. The 4,10-stereochemistry of **7a** and **7b** was deduced from NOE experiments on each isomer, as described previously.[11] These isomers were not separated for the next step of the synthesis. Reduction of this mixture of lactams with lithium aluminium hydride gave a 7:3 mixture of methylenequinolizidines **8a** and **8b** in quantitative yield. Osmium tetroxide-catalyzed periodate oxidation[18,19] of the olefinic bond of quinolizidines **8a** and **8b** under carefully controlled conditions led to a 7:3 mixture of the two diastereomeric alkaloids myrtine **1** and epimyrtine **2**, in 36% yield. Diastereomer separation was achieved by flash column chromatography to give (+)-myrtine **1** and (−)-epimyrtine **2**. These compounds were identified by comparison of their ^{1}H and ^{13}C NMR spectra with the literature data.[3,11] The specific rotations $[\alpha]_D$ were determined to be +13.5 (c 1.45, chloroform) for myrtine (lit.[3] +11.3 (c 2.7, chloroform); lit.[10] +19.3 (c 1.95, chloroform)) and −19 (c 0.4, chloroform) for epimyrtine (lit.[3] −18 (c 5.4, chloroform)).

3. Conformational analysis of myrtine and epimyrtine

Myrtine and epimyrtine can exist as three conformers: one with a *trans* ring junction and two others with a *cis* ring junction as already described by Hootelé et al.[3] Molecular modelling using semi-empirical AM1 calculations established that, contrary to previous assumptions, the unsubstituted *cis*-quinolizidine is more stable than the *trans*-quinolizidine by at least 4.18 kJ mol^{-1}.

Theoretical calculations showed that energies of the three conformers of myrtine are very close to each other and therefore the calculated populations are 29% **1a**, 39% **1b** and 32% **1c**. NMR spectral data were previously considered to be consistent with the presence of conformer **1a** only.[3] This NMR data is, however, also in good agreement with the calculated conformational equilibrium between conformers **1a**, **1b** and **1c**. Epimyrtine exists mainly as the energetically most favorable conformer **2b** (90%) with a *cis* ring junction instead of the *trans* conformer **2a** as previously proposed.[3]



In conclusion, we describe the total synthesis of quinolizidine alkaloids (+)-myrtine **1** and (−)-epimyrtine **2** using intramolecular cyclization of *N*-acyliminium ion (*R*)-**3**. These alkaloids were obtained in five steps from (*S*)-2-(2-hydroxypropyl)allylsilane **4**, with an overall yield of 23% and a high enantiomeric purity. This synthesis constitutes the first total synthesis of naturally occuring (−)-epimyrtine and confirms the configuration 4*R*,10*S* which was assigned previously to this compound.[3]

4. Experimental

NMR spectra were recorded on a Bruker AC 400 spectrometer operating at 400.13 MHz for ^{1}H NMR and 100.61 MHz for ^{13}C NMR. Optical rotations, were recorded on a Jasco model DIP-370 polarimeter. TLC analyses were performed on Merck 60F254 silica gel plates and were visualized using iodine. Flash column chromatography was carried out using Merck silica gel (grade 60, 230–400 mesh).

A molecular modelling study of described molecules was performed using the SYBYL 6.3 software package[20] on a Silicon Graphics R8000 workstation. Structures were built using the building facility of SYBYL and minimized using the Tripos force field MAXIMIN2, *in vacuo*, to provide reasonable standard geometries. Three conformers were considered for compounds **1** and **2**. The geometries of the conformers were deemed to be minimized, by a conjugated gradient method, when there was a minimum energy change of less than 0.021 kJ mol^{-1} for one iteration. The lowest energy conformers thus obtained were submitted to AM1 calculations (MOPAC version 5.0)[21] to optimize their geometry using

the key word 'EF'. The energies were calculated after optimization of all parameters and then compared. The computational procedure of energy caculations using the semi-empirical AM1 method has been validated on calculating the energies of *cis*- and *trans*-decalins and *cis*- and *trans*-9-methyldecalins. The *trans*-decalin has been shown to be more stable than the *cis*-isomer by at least 9.10 kJ mol^{-1} as already reported[22] and the energy of *trans*-9-methyldecalin was evaluated to be higher than the energy of its *cis*-isomer by only 1.46 kJ mol^{-1}. For quinolizidines, contrary to the decalines cases, the *cis*-quinolizidine was determined to be more stable than the *trans*-isomer by 4.18 kJ mol^{-1}.

*4.1. (*R*)-*N*-[1-Methyl-3-(trimethylsilylmethyl)but-3-enyl]glutarimide **5***

To a stirred solution of alcohol **4**[16] (1.2 g; 7.0 mmol), glutarimide (0.79 g; 7.0 mmol) and triphenylphosphine (1.83 g; 7.0 mmol) in anhydrous THF (15 mL) at 0°C under argon was added dropwise a solution of diethyl azodicarboxylate (1.2 g; 7.0 mmol) in THF (1 mL). The reaction mixture was stirred overnight at room temperature and concentrated. The residue was chromatographed over silica gel using ethyl acetate:hexane 3:7 as eluent to give imide **5** (1.1 g) in 67% yield (based on the consumed starting material): $[\alpha]^{25}_{D}$ +29 (c 1.89, $CHCl_3$); IR (cm^{-1}) 1725, 1665, 1630; ^{1}H NMR ($CDCl_3$) δ 5.0–4.90 (1H, m), 4.45 (2H, s), 2.68 (1H, dd, J=10.0, 13.6 Hz), 2.55 (4H, t, J=6.6 Hz), 2.14 (1H, dd, J=13.6, 5.7 Hz), 1.80 (2H, quintet, J=7.5 Hz), 1.42 (2H, s), 1.36 (3H, s, J=6.6 Hz), −0.08 (9H, s); ^{13}C NMR ($CDCl_3$) δ 172.8, 144.8, 109.5, 46.3, 41.7, 33.6, 25.8, 18.0, 17.2, −1.5; exact mass calcd for $C_{14}H_{25}NO_2Si$ 267.165458. Found 267.165518.

*4.2. 6-Hydroxy-1-[1-methyl-3-(trimethylsilyl)but-3-enyl]piperidin-2-one **6***

Sodium borohydride (0.41 g; 10.8 mmol) was added to a stirred solution of imide **5** (0.71 g; 2.7 mmol) in anhydrous methanol (15 mL) at −5°C under argon. The reaction mixture was stirred for 4 h at −5°C. Water was added and the reaction mixture was extracted with methylene chloride. The combined organic layers were dried, concentrated and chromatographed over silica gel (eluted with ethyl acetate:hexane 3:7) to give hydroxylactam **6** isolated as a 1:1 mixture of diastereomers (0.6 g) in 95% yield (based on the consumed starting material): IR (cm^{-1}) 3590 and 1620; ^{1}H NMR ($CDCl_3$) δ 5.0 (1H, m), 4.65 (0.5H, s), 4.60 (0.5H, s), 4.55 (0.5H, s), 4.53 (0.5H, s), 2.70–1.90 (7H, m), 2.80–1.50 (6H, m), 1.35 (1.5H, d, J=8.0 Hz), 1.20 (1.5H, d, J=8.0 Hz), 0.03 (9H, s); ^{13}C NMR ($CDCl_3$) δ 170.5, 169.4, 146.6, 145.5, 109.9, 109.7, 77.1, 48.2, 44.3, 43.2, 42.6, 32.5, 32.3, 30.7, 30.6, 26.4, 26.3, 20.0, 19.3, −1.4; exact mass calcd for $C_{14}H_{27}NO_2Si$: m/z 269.181108. Found m/z 269.181198.

*4.3. 2-Methylene-4-methylquinolizidin-6-ones (4*R*,10*R*)-**7a** and (4*R*,10*S*)-**7b***

To a stirred solution of hydroxylactam (**6**) (0.3 g; 1.1 mmol) in anhydrous methylene chloride (20 mL) at 0°C under argon was added dropwise trifluoroacetic acid (0.51 g; 4.4 mmol). The reaction mixture was stirred for 6 h at 0°C and saturated aqueous sodium bicarbonate was added. The aqueous layer was extracted with methylene chloride. The combined organic layers were dried and concentrated to give crude methylenequinolizidinone **7** (0.2 g; quantitative yield; diastereomeric ratio **7a**:**7b**=7:3) which was used directly in the preparation of quinolizidine **8**. A portion of this crude product was chromatographed over silica gel (eluted with ethyl acetate:hexane 3:7) to give the pure isomers.

7a: IR (cm^{-1}) 1780, 1645; ^{1}H NMR ($CDCl_3$) δ 5.15 (1H, qdd, J=1.8, 5.8, 6.8 Hz), 4.86 (1H, s), 4.78 (1H, s), 3.50–3.30 (1H, m), 2.60–1.40 (10H, m), 1.07 (3H, d, J=6.8 Hz); ^{13}C NMR ($CDCl_3$) δ

169.4, 141.8, 111.1, 51.7, 44.5, 42.4, 39.1, 33.2, 30.5, 19.1, 16.4; exact mass calcd for $C_{11}H_{17}NO$: m/z 179.1310143. Found m/z 179.129332.

7b: IR (cm^{-1}) 1780, 1645; ^1H NMR ($CDCl_3$) δ 4.92–4.86 (2H, m), 4.45 (1H, qdd, J=2.2, 4.7, 6.8 Hz), 3.61 (1H, t, J=12.0 Hz), 2.88–1.25 (10H, m), 1.18 (3H, d, J=6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 173.0, 138.3, 111.4, 53.2, 46.8, 37.9, 37.3, 32.5, 31.0, 20.9, 20.4; exact mass calcd for $C_{11}H_{17}NO$: m/z 179.1310143. Found m/z 179.130177.

*4.4. 4-Methyl-2-methylenequinolizidines (4*R,*10*R*)-**8a** and (4*R,*10*S*)-**8b***

Lithium aluminium hydride (0.09 g; 2.2 mmol) was added to a stirred solution of lactams **7a** and **7b** (0.2 g; 1.1 mmol, 7:3 diastereomeric ratio) in anhydrous THF (10 mL) at room temperature under argon. The reaction mixture was refluxed for 2.5 h, then allowed to warm to room temperature. Ether was added, followed by water (0.15 mL), 15% NaOH (0.15 mL) and water (0.30 mL). The solution was stirred for 1 h and then treated with $MgSO_4$. After filtration, the solution was concentrated to give crude methylenequinolizidine **8** (0.2 g; quantitative yield; 7:3 diastereomeric ratio) which was used directly in the next step. A portion of this crude product was chromatographed to give pure isomers.

8a: IR (cm^{-1}) 2860, 2800 (Bohlmann bands), 1650; ^1H NMR ($CDCl_3$) δ 4.69 (1H, s), 4.58 (1H, s), 3.05 (1H, qu, J=6.0, 1.9 Hz), 2.66 (IH, d, J=11.9 Hz), 2.53 (1H, dd, J=12.8, 5.1 Hz), 2.48–2.25 (2H, m), 2.10 (1H, dt, J=10.4, 2.2 Hz), 2.00–1.85 (3H, m), 1.80–1.35 (5H, m), 0.85 (3H, d, J=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 145.7, 111.4, 57.7, 56.5, 54.2, 44.3, 43.7, 36.0, 28.0, 26.4, 11.9.

8b: IR (cm^{-1}) 2850, 2780 (Bohlmann bands), 1650; ^1H NMR ($CDCl_3$) δ 4.60 (2H, s), 3.28 (1H, br d, J=10.4 Hz), 2.20–1.90 (4H, m), 1.80–1.40 (9H, m), 1.11 (3H, d, J=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 146.2, 106.5, 63.7, 60.2, 51.6, 43.4, 42.3, 33.7, 28.1, 24.3, 20.7.

*4.5. (4*R,*10*R*)-Myrtine **1**, (4*R,*10*S*)-epimyrtine **2***

To a stirred solution of **8** (0.05 g; 0.3 mmol; 7:3 diastereomeric ratio) in 80% acetic acid (5 mL) at 0°C was added sodium (para)periodate (0.2 g; 0.66 mmol) and osmium tetroxide (0.0027 g; 0.011 mmol). The reaction mixture was stirred for 23 h at 8°C. Acetic acid was evaporated to give a residue which was partitioned between methylene chloride and 5% sodium bicarbonate solution. The aqueous layer was extracted with methylene chloride. The combined organic layers were dried and concentrated to give a 7:3 mixture of myrtine **1** and epimyrtine **2** (0.018 g; 36% yield) which were separated by column chromatography.

(+)-Myrtine **1**: $[\alpha]^{25}_D$ +13.5 (c 1.45 chloroform); (lit.[3] $[\alpha]^{28}_D$ +11.3 (c 2.7, chloroform)); IR (cm^{-1}) 2860, 2820, 2775 (Bohlmann bands), 1725; ^1H NMR ($CDCl_3$) δ 3.40 (1H, H-4, d quintet, J=2.3, 6.7 Hz), 2.85 (1H, dd, J=5.9, 13.3 Hz), 2.80 (1H, dt, J=3.9, 12.0 Hz), 2.65 (1H, m), 2.48 (1H, dt, J=2.8, 11.5 Hz), 2.30–2.15 (3H, m), 1.78–1.65 (3H, m), 1.65–1.55 (1H, m), 1.40–1.15 (2H, m), 0.97 (3H, d, J=6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 209.7, 57.3, 53.8, 51.7, 48.9, 48.2, 34.4, 26.0, 23.6, 11.3.

(−)-Epimyrtine **2**: $[\alpha]^{25}_D$ −19 (c 0.4 chloroform); (lit.[3] $[\alpha]^{28}_D$ −18 (c 5.4, chloroform)); IR (cm^{-1}) 2865, 2800, 2760 (Bohlmann bands), 1750; ^1H NMR ($CDCl_3$) δ 3.34 (1H, br d, J=11.0 Hz), 2.50–2.25 (4H, m), 2.24–2.12 (1H, m), 1.90–1.55 (6H, m), 1.50–1.25 (2H, m), 1.20 (3H, d, J=5.7 Hz); ^{13}C NMR ($CDCl_3$) δ 208.7, 62.4, 59.6, 51.3, 50.0, 49.0, 34.4, 26.2, 24.2, 21.0.

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