Use of Nitriles in Synthesis. First Total Synthesis of *ent*-Sachalinol A

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Dedicated with respect and affection to Prof. J. G. Urones on the occasion of his 65th birthday.

Abstract: The total synthesis of *ent*-sachalinol A, has been achieved by utilizing a Sharpless epoxidation and nitrile substitution as the key reactions.

Key words: sachalinol A, Sharpless epoxidation, nitriles, monoterpenes

Recently Kadota et al. described the isolation of Sachalinols A–C, from *Rhodiola Sachalinensis*,[1] as new monoterpenoids. Rosiridin, the glucoside of Sachalinol A, which was previously isolated from *Rhodiola Rosea*,[2] and exhibited non-competitive endopeptidase inhibition against *Flavobacterium* PEP with an IC_{50} of 84 μM (Figure 1).

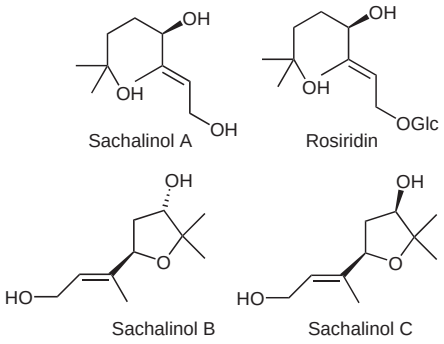
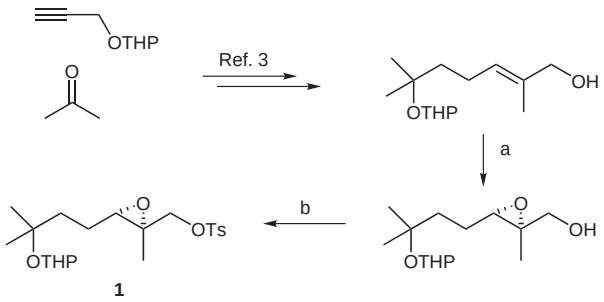


Figure 1

Continuing our studies on iodine cyclization for the synthesis of 2,2,6,6-tetrasubstituted tetrahydropyrans, we have described a straightforward synthesis of epoxide **1**, starting from acetone and propargyl alcohol (Scheme 1).[3]

The synthesis of *ent*-sachalinol A from this tosylepoxide would require the addition of one extra carbon, epoxide-opening, and establishment of the olefin with *E* stereochemistry. Nitrile chemistry could answer these three questions.

Nitriles[4] and α,β-unsaturated nitriles[5] are very useful compounds in organic synthesis. There are several methods for the synthesis of the latter, including: alkenation of aldehydes, displacement of halides from vinyl halides by cyanide ion, transformation of α,β-alkylenenitriles, or



Scheme 1 *Reagents and conditions*: a) L-(+)-DET, Ti(*i*-PrO)$_4$, TBHP, CH_2Cl_2, –23 °C (63%); b) TsCl, py, 0 °C, (92%).[3]

dehydration of oximes.[6] We have experience in epoxide-opening to give allylic alcohols,[7] so we decided to treat epoxide **1**, obtained as a single enantiomer by Sharpless epoxidation (ee >97%, Scheme 1), with NaCN in HMPA,[8] (Scheme 2) followed by deprotection of the tetrahydropyranyl group with *p*-TsOH in MeOH. This gave the α,β-unsaturated nitrile **2**,[9] which has the chiral alcohol and the olefin with the *E* configuration (Scheme 2).[5] Firstly, we decided to carry out the synthetic sequence with the hydroxy group of **2** unprotected. Reduction of the nitrile group was carried out with DIBAL in two steps.[10] The first reduction gave aldehyde **4**, although in low yield (35%), and a second DIBAL reduction gave triol **6** in 40% yield. The spectroscopic properties of **6** were in agreement with those reported for sachalinol A[1] except for the specific rotation being $[\alpha]_D^{20}$ –17.1 (*c* 0.17, MeOH) for the natural compound and $[\alpha]_D^{20}$ –2.0 (*c* 1.0, MeOH), $[\alpha]_D^{20}$ –7.4 (*c* 0.19, MeOH) for **6**. In order to check the enantiomeric excess of **6**, the Mosher diester with (*S*)-(+)-α-methoxy-α-trifluoromethylphenylacetyl chloride (10 equivalents) was obtained,[11] giving only one compound by NMR with a specific rotation of $[\alpha]_D^{20}$ –48.0 (*c* 1.1, $CHCl_3$).

Thus, compound **6** was established as *ent*-sachalinol A and in this manner we have corroborated the structure and stereochemistry of the natural sachalinol A. The difference in the specific rotation of the natural compound sachalinol A and **6** could be understood in terms of the low concentration used for the measurement of the natural product. In order to obtain **6** in better yield, alcohol **2** was protected as its TBDMS derivative **3** under the usual conditions.[12] Double DIBAL reduction as before and final TBAF deprotection[13] gave *ent*-sachalinol in 37% overall yield (from epoxide **1**).

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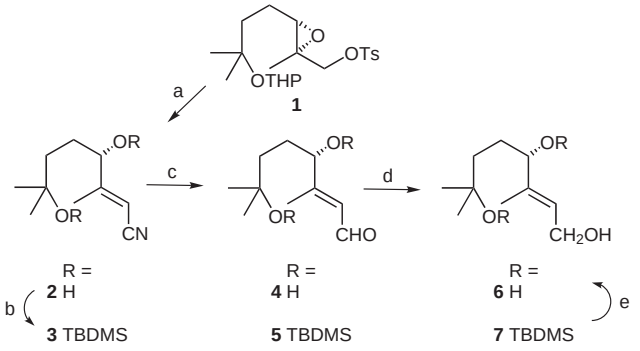
The use of the enantiomer of epoxide **1** obtained by Sharpless epoxidation with D-(–)-DET will lead to the correct stereochemistry for sachalinol A.

In conclusion, we have developed an easy procedure for the synthesis of sachalinol A and its enantiomer.



Scheme 2 *Reagents and conditions*: a) NaCN, HMPA, r.t., then *p*-TsOH, MeOH, r.t. (80%); b) TBDMSOTf, 2,6-Lutidine, THF, r.t. (85%); c) DIBAL (1 equiv), –78 °C, CH_2Cl_2; **2** to **4** (35%), **3** to **5** (85%); d) DIBAL (1 equiv), –78 °C, CH_2Cl_2; **4** to **6** (35%), **5** to **7** (65%); e) TBAF, THF (75%).

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(9) **(2*E*,4*S*)-4,7-Dihydroxy-3,7-dimethyloct-2-enenitrile (2):** NaCN (605 mg, 12.36 mmol) was added to a solution of **1** (1.7 g, 4.12 mmol) in HMPA (8 mL). After stirring for 3 h, the mixture was diluted with H_2O (150 mL). The aqueous layer was extracted with EtOAc (5 × 100 mL) and the combined organic extracts were washed with 10% aq HCl (3 × 50 mL), 5% aq $NaHCO_3$ (3 × 50 mL), and brine (3 × 50 mL). The aqueous acidic layer was extracted with EtOAc (100 mL) and the combined organic extracts washed again with 5% aq $NaHCO_3$ (3 × 10 mL) and brine (3 × 10 mL). The organic solution was dried and the filtrate was concentrated to give 1.6 g of the crude product, which was dissolved in MeOH (20 mL). Then, a catalytic amount of *p*-TsOH (75 mg, 0.41 mmol) was added and, after stirring for 2 h, the reaction was quenched by the addition of $NaHCO_3$ (100 mg). The MeOH was evaporated and the mixture was dissolved in EtOAc, filtered, and concentrated to give nitrile **2** (605 mg, 80%), which was used in the next step without further purification; $[\alpha]_D^{20}$ –27.0 (*c* 2.0, $CHCl_3$). IR (film): 3400 (br), 2970–2870, 2222, 1632, 1441, 1381, 1215, 1152, 1090, 910 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 5.55 (1 H, s, H-2), 4.18 (1 H, m, H-4), 2.01 (3 H, s, H-10), 1.9–1.2 (4 H, m, H-5, H-6), 1.24 (6 H, s, H-8, H-9). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.71 (C-10), 29.35 (C-5), 29.53 (C-9), 29.57 (C-8), 38.36 (C-6), 70.76 (C-7), 74.43 (C-4), 94.95 (C-2), 117.27 (C-1), 166.07 (C-3). HRMS-EI: *m*/*z* calcd for $C_{10}H_{17}O_2N$ $[M]^+$: 183.1259; found: 183.1237.
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