

SYNTHESIS OF NATURALLY OCCURRING (R)-(+)-MUSCOPYRIDINE

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Dedicated to Professor Herbert C. Brown on his 70th birthday

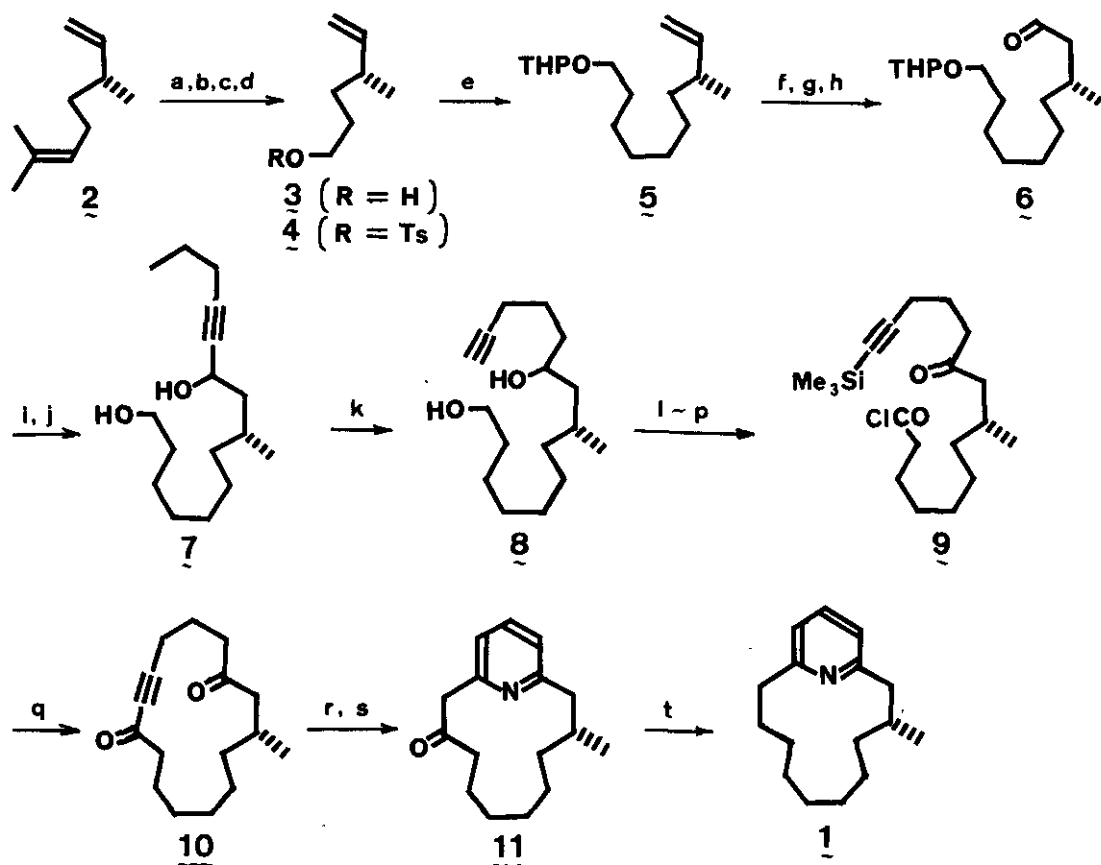
Abstract — Incorporation of the chiral center of (R)-4-methyl-5-hexenyl tosylate gives the title compound. The synthesis establishes the absolute configuration of the natural product. The title compound is also obtained from (Z)-1,2-dehydromuscovopyridine by asymmetric reduction with chiral alkylboranes.

Synthesis of muscovopyridine with definite configuration is significant for the determination of the configuration of the natural product.¹⁻⁴ This paper describes the preparation of (R)-muscovopyridine (1), which has been found to be identical with the natural (+)-isomer. An asymmetric synthesis of (+)-muscovopyridine with chiral alkylboranes is added lastly.

The chiral starting material chosen was (R)-3,7-dimethyl-1,6-octadiene (2)⁵, whose selective ozonolysis at -78°C followed by reduction gave (R)-4-methyl-5-hexen-1-ol (3). The corresponding tosylate 4 was coupled with 4-(oxacyclohex-2-yloxy)butylmagnesium bromide under the catalytic action of dilithium tetrachlorocuprate.⁶

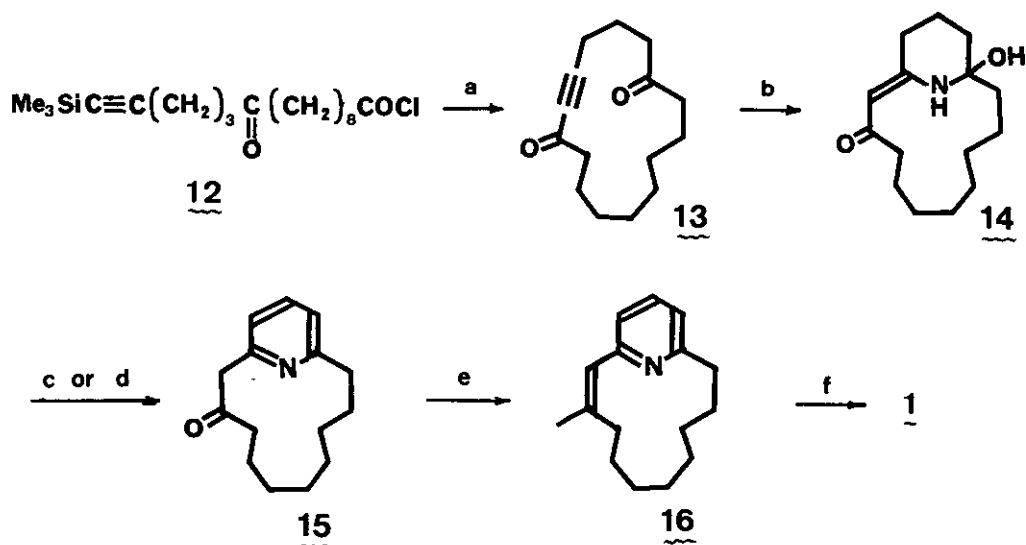
The resulting unsaturated compound 5 was transformed into an aldehyde 6 by hydroboration with bis(3-methyl-2-butyl)borane followed by usual oxidation. Treatment of 6 with 1-pentynylmagnesium bromide gave the diol 7 in 89% yield after hydrolysis of the reaction mixture. The terminal acetylenic diol 8 was obtained in 80% yield by treatment with potassium 3-aminopropylamide.⁷ During the migration of triple bond, the chiral center is postulated to be conserved untouched.⁸ Acyl chloride 9 was prepared from 8 in almost quantitative yield by a sequence of reactions:⁷ (1) replacement of ethynyl hydrogen with trimethylsilyl by successive treatment with ethylmagnesium bromide, chlorotrimethylsilane, and dil. HCl, (2) oxidation of both hydroxy groups with chromic acid (Jones reagent) affording keto acid, and (3)

treatment with oxalyl chloride. The subsequent aluminium chloride-catalyzed cyclization⁷ gave (R)-9-methyl-2-cyclopentadecyne-1,7-dione (10) in 82% yield. Transannular insertion of one nitrogen by means of aqueous ammonia⁹ followed by thermolysis¹⁰ gave 2-oxomuscovopyridine (11) in 72% overall yield. Wolff-Kishner reduction afforded (R)-muscovopyridine (1) in 85% yield. As the chiral center is not touched throughout the sequence of transformation, the resulting product, (R)-muscovopyridine, is anticipated to have high optical purity¹¹ and the observed optical rotation could be used for the determination of configuration. Comparison of the rotational sign of the product with those of the reported ones¹ establishes that natural muscovopyridine has R configuration.



a. O₃; b. Me₂S; c. LiAlH₄; d. TsCl-pyridine (3 + 4); e. BrMg(CH₂)₄OTHP/Li₂CuCl₄; f. (Me₂CHCHMe)₂BH; g. H₂O₂-aq. NaOH; h. pyridium chlorochromate; i. n-PrC≡CMgBr; j. aq. MeOH/TsOH; k. KNH(CH₂)₃NH₂; l. EtMgBr; m. Me₃SiCl; n. dil. HCl; o. CrO₃-H₂SO₄ (Jones reagent); p. (COCl)₂; q. AlCl₃/high dilution method; r. aq. NH₃; s. Δ (prep. glc); t. H₂NNH₂·H₂O/KOH

Analogous cyclization of 15-trimethylsilyl-10-oxo-14-pentadecynoyl chloride (12) gave 2-cyclopentadecyne-1,7-dione (13) in 80% yield. Treatment with aqueous ammonia afforded the bicyclic ketone 14 in 96% yield.¹² Preparative glc gave an aromatized pyridine derivative 15 in 82% yield. Alternatively, 15 was also obtained in 76% yield by treatment of 14 with 1 eq. of tetrachloro-*o*-benzoquinone in benzene solution at reflux for 2.5 h. Reaction of the ketone 15 with excess methyl lithium in THF at room temperature gave a (Z)-olefin 16 in 90% glc yield.¹³ The ketone 15 was recovered quantitatively when 1 eq. of MeLi was applied. This fact is explained by assuming that the ketone 15 is readily enolized by the first eq. of MeLi and then the methyl group is introduced with simultaneous loss of Li₂O. Reaction in ether, on the other hand, afforded the methylated alcohol¹⁴ with contamination of the starting material 15. This observation shows that in ether solution MeLi does not react with lithium enolate under the applied reaction conditions. Reduction of the olefin 16 with monoisopinocampheylborane¹⁵ obtained from (-)- α -pinene afforded (+)-muscovydine.^{16,17}



a. AlCl_3 /high dilution method; b. aq. NH_3 ; c. Δ (prep. glc); d. tetrachloro-*o*-benzoquinone; e. MeLi/THF; f. H_2B (monoisopinocampheylborane)



ACKNOWLEDGEMENT

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REFERENCES AND NOTES

1. The optical rotation of natural muscopyridine was reported ($[\alpha]_D^{23} +17.4^\circ$, ref. 2). Optical resolution of the racemic product afforded the (+)-isomer ($[\alpha]_D^{25} +13.31^\circ$, ref. 3). The absolute configuration has not been established to our best knowledge.
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4. Synthesis of muscopyridine in its racemic form: (a) ref. 2. (b) K. Tamao, S. Kodama, T. Nakatsuka, Y. Kiso, and M. Kumada, J. Am. Chem. Soc., 1975, 97, 4405. (c) H. Saimoto, T. Hiyama, and H. Nozaki, Tetrahedron Lett., 1980, 21, 3897.
5. R. Rienäcker and G. Ohloff, Angew. Chem., 1961, 73, 240.
6. G. Fouquet and M. Schlosser, Angew. Chem., 1974, 86, 50.
7. K. Utimoto, M. Tanaka, M. Kitai, and H. Nozaki, Tetrahedron Lett., 1978, 2301.
8. Analogous conservation of the configuration of the methylated carbon was reported in ref. 7.
9. Treatment with aq. ammonia gave a dihydro compound of 11 predominantly.
10. Thermolysis in a preparative glc apparatus gave good results conveniently.
11. Thermolysis of (-)-cis-pinane ($[\alpha]_D^{25} -20.4^\circ$, neat, 84% e.e.) gave the starting material 2 ($[\alpha]_D^{25} -8.0^\circ$, neat, 82% e.e.). The optical rotation of the resulting (R)-muscopyridine: $[\alpha]_D^{25} +11.5^\circ$, c = 4.55, d = 0.1, CHCl₃. Determination of the enantiomeric ratio by Eu(hfc)₃-shifted nmr was unsuccessful.
12. The structure was estimated by ir and nmr spectra.
13. The homogeneity of the resulting olefin 16 was confirmed by glc and tlc. The stereochemistry was determined by ¹H-nmr as well as ¹³C-nmr spectra.
14. Dehydration produced a mixture of isomeric olefins.
15. H. C. Brown, J. R. Schwier, and B. Singaram, J. Org. Chem., 1978, 43, 4395. (-)-α-Pinene ($[\alpha]_D^{22} -42^\circ$, Aldrich Chemical Co.) was used.
16. Simple workup with aq. NaHCO₃ and no oxidative treatment gave muscopyridine, $[\alpha]_D^{20} +3.6^\circ$, 21% e.e. based on the reported optical rotation (ref. 2).
17. Reduction with diisopinocampheylborane prepared from (-)-α-pinene provided the (+)-muscopyridine ($[\alpha]_D^{25} +2.3^\circ$).

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