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An Efficient Synthesis of 15-Oxygenated T-Type Spirovetivanes. Its Application to the Synthesis of (±)-[8,8-$^2H_2$]Isolubimin[1)]

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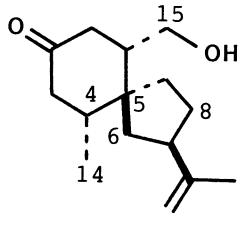
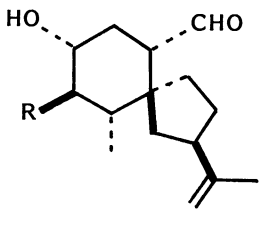
(4RS,7RS)-11-Hydroxy-15-norsolavetivane, a versatile intermediate for the synthesis of all 15-oxygenated T-type spirovetivanes, has been synthesized with high stereoselectivity. The synthesis has also been applied to preparation of (±)-[8,8-$^2H_2$]isolubimin.

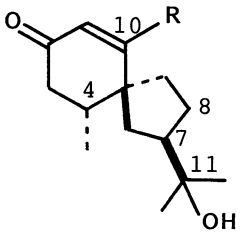
15-Oxygenated T-type spirovetivane sesquiterpenes,[2)] represented by isolubimin (1), lubimin (2), and oxylubimin (3), are produced by potato tubers infected with fungi and qualified as phytoalexins.[3)] We have recently reported the first total synthesis of (±)-2, (±)-3, and their related compounds via (4RS,7RS)-11-hydroxy-15-norsolavetivane (±)-(4) as a versatile intermediate, which has been prepared by π-cyclization reaction of anti-8-methylbicyclo[2.2.2]octene diol monomesylates[4)] (5). However, this crucial reaction proceeded with low stereoselectivity at C-7 of the cyclized products, resulting in formation of (±)-4 only in 35% isolated yield. On the other hand, the corresponding reaction of the 5-methyl derivatives (6) led to exclusive formation to (4RS,7RS)-11-hydroxysolavetivane (±)-(7) in a high yield (63-69%).[5)] These results suggested that introduction of an easily removable functional group into C-5 of compounds 5 might increase the stereoselectivity in the cyclization reaction. We disclose herein a highly efficient synthesis of (±)-4 as well as its application to the synthesis of (±)-[8,8-$^2H_2$]isolubimin (±)-(1-D), which will be useful for studies of the biosynthesis.[6)]



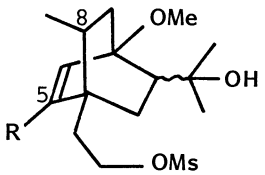
1 8,8-H_2
1-D 8,8-$^2H_2$



2 R=H
3 R=OH

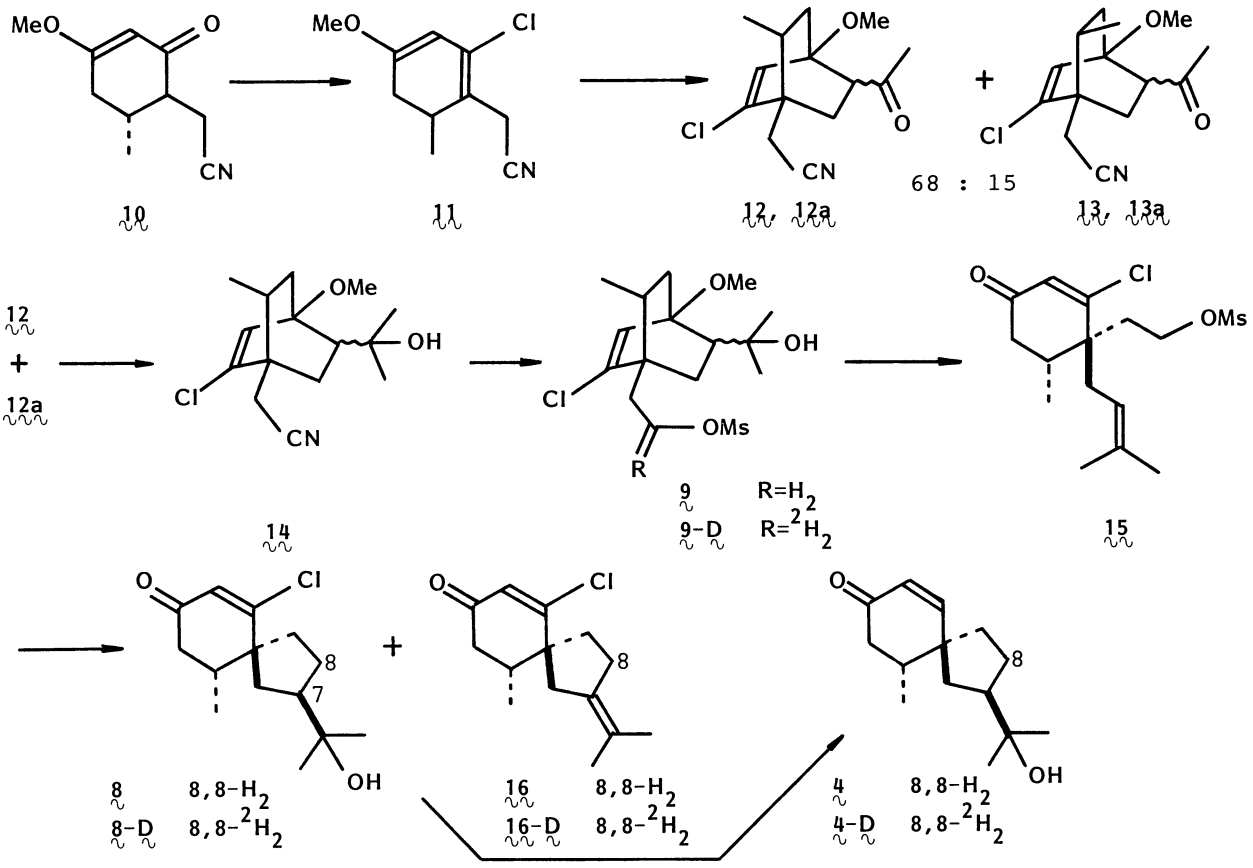


4 R=H, 7 R=Me
8 R=Cl



5 R=H, 6 R=Me
9 R=Cl

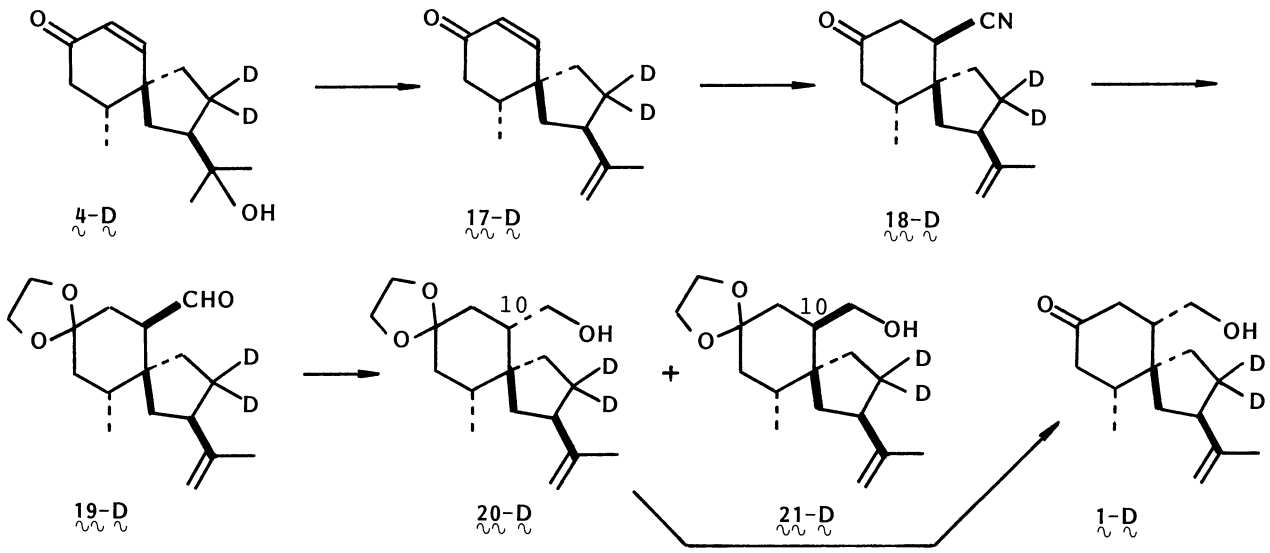
The present synthesis involves the stereoselective formation of (4RS,7RS)-10-chloro-11-hydroxy-15-norsolavetivane (±)-(8) from 5-chloro derivatives (±)-(9)



Scheme 1.

of 5 at the relevant cyclization stage. Thus readily available 4-methoxy-6-methyl-2-oxo-3-cyclohexenylacetonitrile[7] (10) was treated with catechylphosphotrichloride[8] and base (DBU, benzene, reflux, 2 h) to give chlorodienyl ether (11) (98%)[9] (Scheme 1). Cycloaddition of 11 with methyl vinyl ketone (xylene, 150 °C, 7 d) afforded a mixture of four stereoisomeric adducts, which was separated by chromatography over silica gel to give the anti,endo- (12), anti,exo- (12a), syn,endo- (13), and syn,exo-adducts (13a) in 40, 28, 3, and 12% yields, respectively.[10] A mixture of the anti-adducts (12 and 12a) was treated with methyllithium (ether-THF, -78 °C, 2 h) to yield smoothly oxyisopropyl cyanides (14), which were converted in a three-step process (DIBAH; $NaBH_4$; $MeSO_2Cl$) into the corresponding monomesylates (9) (92%). The cyclization in question proceeded most effectively as follows; the compounds (9), when treated with formic acid (20 °C, 2 h), were transformed into prenyl mesylate (15), which was heated with oxalic acid (a 5:1 mixture of MIBK and water, 130 °C, 8 h) to afford 8 with the desired (7RS)-configuration in 72% yield along with its dehydrated product (16) (19%). It should be noted that any trace amount of the corresponding (7SR)-isomer was not detected by HPLC. Compound 8 was then reduced by a modification of the Heathcock procedure[11] (Zn-Ag couple, MeOH-AcOH, 20 °C, 1 h) to the corresponding dechloro enone (4) in a quantitative yield, which was identical with an authentic sample[4] in all respects. The present result indicates that the intermediate (±)-4 has been prepared in 44.1% overall yield from 10 (9 steps).

The title compound, isolubimin[12] (1), has been considered to play an important role in the biogenetic pathway of various spirovetivane phytoalexins in the Solanaceae family.[13] Thus the present result was applied to the synthesis of 8,8-deuterated (±)-isolubimin (±)-[8,8-$^2H_2$](1) [(±)-1-D] for the biosynthetic studies. The synthesis was commenced by transformation of 14 into the doubly deuterated mesylates (9-D) in a four-step process [Jones oxidation; CH_2N_2; $LiAlD_4$ (D_2-content, over 98%); $MeSO_2Cl$] (78%). The mesylates were treated successively with formic acid (20 °C, 1 h) and with oxalic acid (a 1:2 mixture of MeCN and water, 90 °C, 1 h) to give (±)-8-D in 68% yield with (±)-16-D (12%), which was smoothly converted into the deuterated 15-norsolavetivane (±)-(4-D). The ^1H NMR spectrum was indistinguishable from that of the corresponding cold sample (4), while the EI-MS spectrum indicated the D_2-content to be ca. 100%. The compound (4-D) was submitted to dehydration (Al_2O_3-Py, 220 °C, 8 min) into deuterated norsolavetivone (±)-(17-D), which, on hydrocyanation (HCN, Et_3Al, THF, 0 °C, 45 min),[14] furnished the cyano ketone (±)-(18-D) as the sole product [39% from (±)-4-D] (Scheme 2). The compound (18-D) was converted by careful acetalization [$(CH_2OH)_2$, PPTS, benzene, 85 °C, 16 h] and subsequent reduction (DIBAH, ether, 0 °C, 1 h) into formyl ethylene acetal (±)-(19-D) (59%), which was epimerized under basic conditions (5% KOH-MeOH) to yield an inseparable 2:1 mixture of 10α- and 10β-formyl (19-D) compounds. The mixture was reduced with sodium borohydride to give a mixture of epimeric alcohols, from which the 10βH- (±)-(20-D) and 10αH-alcohols (±)-(21-D) were isolated in 49 and 28% yields, respectively. The former (20-D) was finally deacetalized (PPTS, aq acetone, 70 °C, 2 h) to give (±)-[8,8-$^2H_2$]isolubimin (±)-(1-D), oil, in 55% yield. The deuterated compound thus obtained revealed the spectra differing from those of (±)-isolubimin only in the following: MS, m/z 238 (M^+, 20.8%) and 236 (M^+ - 2, 0%), (D_2-content, ca. 100%); IR, 2200 and 2110 cm^{-1}.[15] The synthesis involved 16 steps and the overall yield amounted to 2.2% from 10. The feeding experiments with (±)-1-D in healthy and/or in diseased potato tubers are under investigation.



Scheme 2.

References

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2) We designate tentatively "T-type spirovetivanes" as the spirovetivane sesquiterpenes possessing the trans-configuration between the C-4-C-14 and C-5-C-6 bonds. Cf., A. Murai, Yuki Gosei Kagaku Kyokai Shi, 39, 893 (1981).

3) Cf., J. Kuć, "Phytoalexins," ed by J. A. Bailey and J. W. Mansfield, Blackie, Glasgow and London (1982), Chap. 3; T. Masamune, M. Takasugi, and A. Murai, Yuki Gosei Kagaku Kyokai Shi, 43, 217 (1985); A Murai, Pure Appl. Chem., in press.

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5) A. Murai, S. Sato, and T. Masamune, Tetrahedron Lett., 22, 1033 (1981); idem., Bull. Chem. Soc. Jpn., 57, 2276 (1984).

6) Cf., A. Murai, S. Sato, A. Osada, N. Katsui, and T. Masamune, J. Chem. Soc., Chem. Commun., 1982, 32; A. Murai, Y. Yoshizawa, M. Ikura, N. Katsui, and T. Masamune, ibid., 1986, 891.

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9) All new compounds reported herein were well characterized and gave satisfactory spectra.

10) 12: mp 67-68 °C; ^{1}H NMR ($CDCl_3$) δ=0.88 (3H, d, J=6.8 Hz), 2.19 (3H, s), 3.08 (1H, dd, J=9.3 and 5.4 Hz), and 6.26 (1H, s). 12a: mp 121-123 °C; ^{1}H NMR ($CDCl_3$) δ=0.83 (3H, d, J=6.8 Hz), 2.25 (3H, s), 3.07 (1H, ddd, J=9.3, 5.9, and 2.0 Hz), and 6.46 (1H, s). 13: oil; ^{1}H NMR ($CDCl_3$) δ=1.11 (3H, d, J=6.8 Hz), 2.18 (3H, s), 3.03 (1H, dd, J=9.3 and 5.4 Hz), and 6.21 (1H, s). 13a: mp 86-88 °C; ^{1}H NMR ($CDCl_3$) δ=1.20 (3H, s), 2.25 (3H, s), 3.00 (1H, ddd, J=11.2, 5.4, and 2.0 Hz), and 6.43 (1H, s).

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13) J. B. Stothers, Pure Appl. Chem., 53, 1241 (1981).

14) W. Nagata, Nippon Kagaku Zasshi, 90, 837 (1969).

15) (±)-1-p: IR (neat) 3460, 3085, 2200, 2110, 1715, 1650, and 885 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.99 (3H, d, J=6.2 Hz), 1.75 (3H, s), 3.51 (1H, dd, J=10.5 and 8.1 Hz), 3.98 (1H, dd, J=10.5 and 3.4 Hz), and 4.71 (2H, br s).

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