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An Efficient Synthesis of 15-Oxygenated T-Type Spirovetivanes. Its Application to the Synthesis of $(\pm) - [8, 8-^{2}H_{2}]$ Isolubimin¹⁾

Akio MURAI,^{*} Hiroshi MIYAZAKI, Katsuyuki WATANABE, and Tadashi MASAMUNE Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060

(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 $has also been applied to preparation of <math>(\pm)-[8,8-^{2}H_{2}]$ isolubimin.

15-Oxygenated T-type spirovetivane sesquiterpenes, 2) represented by isolubimin $(\frac{1}{4})$, lubimin $(\frac{2}{2})$, and oxylubimin $(\frac{3}{2})$, are produced by potato tubers infected with fungi and qualified as phytoalexins.³⁾ We have recently reported the first total synthesis of $(\pm)-2$, $(\pm)-3$, and their related compounds via (4RS,7RS)-11-hydroxy-15-norsolavetivane $(\pm) - (4)$ as a versatile intermediate, which has been prepared by *m*-cyclization reaction of <u>anti-8-methylbicyclo[2.2.2]octene</u> diol monomesylates⁴⁾ (5). However, this crucial reaction proceeded with low stereoselectivity at C-7 of the cyclized products, resulting in formation of (\pm) -4 only in 35% isolated yield. On the other hand, the corresponding reaction of the 5methyl derivatives (6) led to exclusive formation to (4RS,7RS)-11-hydroxysolavetivane $(\pm) - (7)$ 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 (t) - 4 as well as its application to the synthesis of $(\pm) - [8, 8 - {}^{2}H_{2}]$ isolubimin $(\pm) - (\pm - p)$, which will be useful for studies of the biosynthesis.65



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



Scheme 1.

of 5 at the relevant cyclization stage. Thus readily available 4-methoxy-6methyl-2-oxo-3-cyclohexenylacetonitrile⁷⁾ (10) was treated with catechylphosphotrichloride⁸⁾ and base (DBU, benzene, reflux, 2 h) to give chlorodienyl ether (11) (98%)⁹⁾ (Scheme 1). Cycloaddition of $\frac{11}{24}$ 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 <u>anti</u>-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; NaBH₄; MeSO₂Cl) into the corresponding monomesylates (9) (92%). The cyclization in question proceeded most effectively as follows; the compounds (2), 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 procedure¹¹⁾ (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 sample⁴⁾ in all respects. The present result indicates that the intermediate $(\pm)-4$ has been prepared in 44.1% overall yield from 10 (9 steps).

The title compound, isolubimin¹²⁾ (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 (\pm) -isolubimin (\pm) -[8,8-²H₂](1) [(\pm)-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; CH2N2; LiAlD4 (D₂-content, over 98%); MeSO₂Cl] (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 $(\pm) - (4-D)$. The ¹H NMR spectrum was indistinguishable from that of the corresponding cold sample (4), while the EI-MS spectrum indicated the D2-content to be ca. 100%. The compound (4-D) was submitted to dehydration (Al₂O₃-Py, 220 °C, 8 min) into deuterated norsolavetivone (±)-(17-D), which, on hydrocyanation (HCN, Et₃Al, THF, 0 °C, 45 min),¹⁴⁾ furnished the cyano ketone (±)-($\frac{18}{\sqrt{3}}$ - $\frac{10}{\sqrt{3}}$) as the sole product [39% from (±)-4-D] (Scheme 2). The compound (18-D) was converted by careful acetalization [(CH₂OH)₂, PPTS, benzene, 85 °C, 16 h] and subsequent reduction (DIBAH, ether, 0 °C, 1 h) into formyl ethylene acetal $(\pm) - (19-D)$ (59%), which was epimerized under basic conditions (5% KOH-MeOH) to yield an inseparable 2:1 mixture of $10\,\alpha\text{-}$ and 10 B-formyl (19-D) compounds. The mixture was reduced with sodium borohydride to give a mixture of epimeric alcohols, from which the 10β H- (±)-(20-D) and 10α Halcohols $(\pm) - (21 - D)$ 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- 2 H₂]isolubimin (±)-(1-D), oil, in 55% yield. The deuterated compound thus obtained revealed the spectra differing from those of (\pm) -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 $(\pm)-1-D$ in healthy and/or in diseased potato tubers are under investigation.



Scheme 2.

References

- Part XLIII of "Studies on the Phytoalexins" and Part XXI of "Synthetic Studies of Rishitin and Related Compounds." Part XLII of the former series, A. Murai, Y. Yoshizawa, N. Katsui, S. Sato, and T. Masamune, Chem. Lett., <u>1986</u>, 771: Part XX of the latter series, A. Murai and T. Masamune, ibid., <u>1984</u>, 1143.
- We designate tentatively "T-type spirovetivanes" as the spirovetivane sesquiterpenes possessing the <u>trans</u>-configuration between the C-4-C-14 and C-5-C-6 bonds. <u>Cf.</u>, A. Murai, Yuki Gosei Kagaku Kyokai Shi, <u>39</u>, 893 (1981).
- 3) <u>Cf</u>., 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, <u>43</u>, 217 (1985); A Murai, Pure Appl. Chem., in press.
- A. Murai, S. Sato, and T. Masamune, J. Chem. Soc., Chem. Commun., <u>1982</u>, 512, 513; idem., Bull. Chem. Soc. Jpn., <u>57</u>, 2286, 2291 (1984).
- 5) A. Murai, S. Sato, and T. Masamune, Tetrahedron Lett., <u>22</u>, 1033 (1981); idem., Bull. Chem. Soc. Jpn., 57, 2276 (1984).
- 6) <u>Cf</u>., A. Murai, S. Sato, A. Osada, N. Katsui, and T. Masamune, J. Chem. Soc., Chem. Commun., <u>1982</u>, 32; A. Murai, Y. Yoshizawa, M. Ikura, N. Katsui, and T. Masamune, ibid., <u>1986</u>, 891.
- 7) A. Murai, S. Sato, and T. Masamune, J. Chem. Soc., Chem. Commun., <u>1981</u>, 904; idem., Bull. Chem. Soc. Jpn., <u>57</u>, 2282 (1984).
- 8) K. Schank, B. Eisert, and J. H. Felzmann, Chem. Ber., 99, 1414 (1966).
- All new compounds reported herein were well characterized and gave satisfactory spectra.
- 10) 12: mp 67-68 °C; ¹H NMR (CDCl₃) δ =0.88 (3H, d, <u>J</u>=6.8 Hz), 2.19 (3H, s), 3.08 (1H, dd, <u>J</u>=9.3 and 5.4 Hz), and 6.26 (1H, s). 12a: mp 121-123 °C; ¹H NMR (CDCl₃) δ =0.83 (3H, d, <u>J</u>=6.8 Hz), 2.25 (3H, s), 3.07 (1H, ddd, <u>J</u>=9.3, 5.9, and 2.0 Hz), and 6.46 (1H, s). 13: oil; ¹H NMR (CDCl₃) δ =1.11 (3H, d, <u>J</u>=6.8 Hz), 2.18 (3H, s), 3.03 (1H, dd, <u>J</u>=9.3 and 5.4 Hz), and 6.21 (1H, s). 13a: mp 86-88 °C; ¹H NMR (CDCl₃) δ =1.20 (3H, s), 2.25 (3H, s), 3.00 (1H, ddd, <u>J</u>=11.2, 5.4, and 2.0 Hz), and 6.43 (1H, s).
- 11) R. D. Clark and C. H. Heathcock, J. Org. Chem., 41, 636 (1976).
- 12) N. Katsui, F. Yagihashi, A. Murai, and T. Masamune, Chem. Lett., <u>1978</u>, 1205; idem., Bull. Chem. Soc. Jpn., <u>55</u>, 2424 (1982); A. Stoessl, J. B. Stothers, and E. W. B. Ward, Can. J. Chem., <u>56</u>, 645 (1978).
- 13) J. B. Stothers, Pure Appl. Chem., <u>53</u>, 1241 (1981).
- 14) W. Nagata, Nippon Kagaku Zasshi, <u>90</u>, 837 (1969).
- 15) $(\pm) -1 \mathbb{Q}$: IR (neat) 3460, 3085, 2200, 2110, 1715, 1650, and 885 cm⁻¹; ¹H NMR (CDCl₃) δ =0.99 (3H, d, <u>J</u>=6.2 Hz), 1.75 (3H, s), 3.51 (1H, dd, <u>J</u>=10.5 and 8.1 Hz), 3.98 (1H, dd, <u>J</u>=10.5 and 3.4 Hz), and 4.71 (2H, br s).

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