CHEMISTRY LETTERS, pp. 299-302, 1981.

SYNTHESIS OF (±)-3,3-ETHYLENEDIOXY-14α-HYDROXY-5-PICRASENE-11,16-DIONE, A 14αH-PICRASANE DERIVATIVE

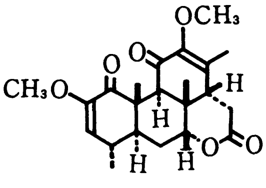
Tadashi HONDA, Tatsushi MURAE, Shinya OHTA, Yohei KURATA,
Hisashi KAWAI, Takeyoshi TAKAHASHI,* Akiko ITAI,† and Yoichi IITAKA†
Department of Chemistry, Faculty of Science, The University of Tokyo,
†Faculty of Pharmaceutical Sciences, The University of Tokyo,
Hongo, Bunkyo-ku, Tokyo 113

(±)-3,3-Ethylenedioxy-14α-hydroxy-5-picrasene-11,16-dione possessing a 14αH-5-picrasene framework has been synthesized.

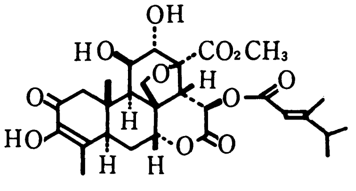
The bitter principles "quassinoids" isolated from the plants of the family Simaroubaceae[1)] have attracted interest because of their wide spectrum of biological properties, including antileukemic activity.[1,2)] A number of synthetic approaches to quassinoids, such as quassin (**1**)[3)] and bruceantin (**2**),[2a)] have been described,[4)] the main problem of these syntheses being the construction of their highly oxygenated picrasane skeletons. We wish to report the synthesis of (±)-3,3-ethylenedioxy-14α-hydroxy-5-picrasene-11,16-dione (**3**) with a 14αH-picrasane framework, which contains five (C-4, C-7, C-8, C-9, and C-10) of the seven chiral centers as those of quassin (**1**).

Robinson annulation of the known keto alcohol (**4**)[5)] with ethyl vinyl ketone gave a tricyclic keto alcohol (**5**) in 41% yield, an ethylene acetal (**6**) being obtained in 88% yield by acetalization of **5**. Collins oxidation of **6** afforded a diketone monoethylene acetal (**7**) in 89% yield. A cis-relationship between the two tertiary methyl groups for **5**, **6**, and **7** received support from oxidation of **5** with the Jones reagent to give a tricyclic diketone (**8**), which was found to be identical with the ketone derived from the known acetal (**9**)[6)] by acid hydrolysis.

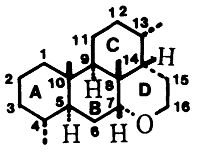
The ketone (**7**) was treated with 1 equivalent mole of lithium diisopropylamide in tetrahydrofuran and methylated with methyl iodide at room temperature for 30 min to give a monomethylated product (**10**) in 84% yield. Reduction of **10** with lithium



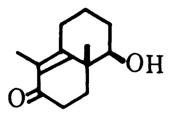
1



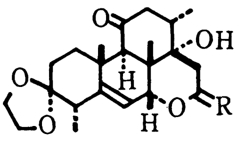
2



Picrasane

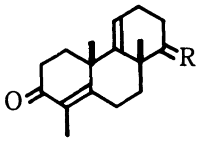


4



3 R = O

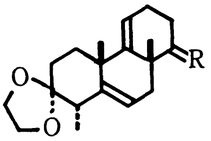
17 R = H, OH



5 R = α-H, β-OH

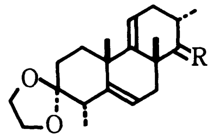
8 R = O

9 R = $-O(CH_2)_2O-$



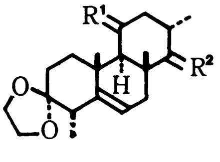
6 R = α-H, β-OH

7 R = O



10 R = O

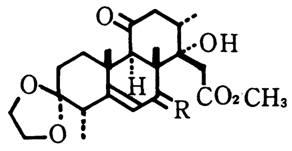
11 R = α-H, β-OH



12 R¹ = α-OH, β-H

R² = α-H, β-OH

13 R¹ = O, R² = O



14 R = H_2

16 R = O

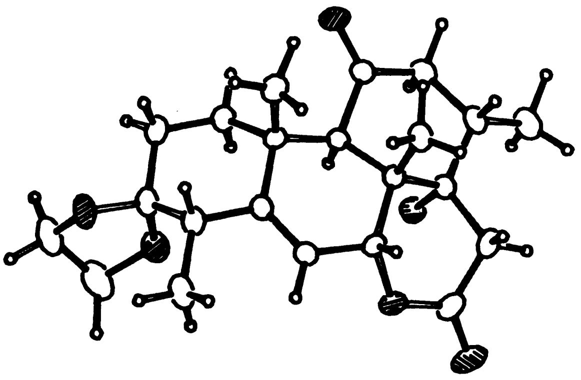
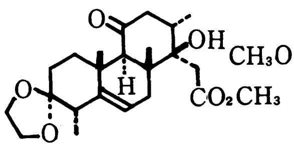
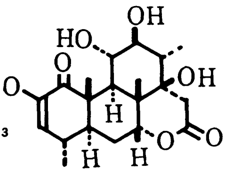


Fig. 1

o:Hydrogen, ●:Oxygen, ○:Carbon



15



18

aluminium hydride in ether at 0 °C gave an alcohol (**11**) in 99% yield. In the ^{1}H n.m.r. spectrum of **11**, a C-14 proton resonated as a doublet with J=11 Hz; this shows the C-14 hydroxyl and the C-13 methyl are both in an equatorial conformation and leads to 14β and 13α configurations for these groups, respectively. Selective introduction of a hydroxyl group to the C-11 position of **11** was carried out by hydroboration with diborane in tetrahydrofuran at 0 °C followed by treatment with alkaline hydrogen peroxide to afford a diol (**12**) in 68% yield. Observed coupling constant (J=11 Hz) between the C-9 and C-11 protons is compatible with the structure (**12**) with C-11α (equatorial) hydroxyl and C-9α (axial) proton.

Oxidation of **12** with the Collins reagent gave a diketone (**13**) in 84% yield.

After several trials, it was eventually found that treatment of the diketone (**13**) with dilithioacetate7) in tetrahydrofuran at 0 °C gave, after esterification with diazomethane, a pair of diastereomers (**14** and **15**) in 71% and 24% yields, respectively. The major ester (**14**) was oxidized with the Collins reagent to give an α,β-unsaturated ketone (**16**) in 44% yield. Reduction of **16** with sodium borohydride in ethanol at 0 °C gave a hemiacetal (**17**) in 22% yield, which afforded the lactone (**3**) in 27% yield by oxidation with silver(I) oxide. When **17** was treated with the Jones reagent, **3** was obtained in 80% yield.

For a confirmation of the stereochemistry of the chiral centers in the lactone (**3**), a single-crystal X-ray analysis has been carried out. Crystals of racemic **3** belong to the triclinic space group P1. The unit cell parameters are a=13.095(6), b=12.425(6), c=8.204(4) Å, α=108.16(4), β=87.51(4), γ=100.19(4)° with two molecules of **3** and two molecules of ethyl acetate in it. The intensity data were collected on a Philips PW1100 four-circle diffractometer using graphite-monochromated Cu Kα radiation. The structure was solved by the direct method using program MULTAN and refined by the method of block-diagonal least-squares assuming anisotropic thermal vibrations. The final R-factor was 0.062 for 3560 non-zero, independent reflections including hydrogen atoms with isotropic temperature factors. The molecular structure of the lactone (**3**) as depicted in Figure 1 reveals that rings A and C are in chair form and rings B and D in boat one.

Further studies for the synthesis of quassinoids including nigakilactone M (**18**)8) are under way.

Characterization of racemic **5-8**, **10-17**, and **3** is as follows; these compounds showed the IR and ^{1}H n.m.r. spectral data compatible with their structures, respectively; **5**: mp 142-143 °C, $C_{17}H_{24}O_2$,9) MS m/e 260 (M^+); **6**: mp 198-199 °C, $C_{19}H_{28}O_3$ (MW 304.2002);10) **7**: mp 120-122 °C, $C_{19}H_{26}O_3$,9) MS m/e 302 (M^+); **8**: mp 116 °C, $C_{17}H_{22}O_2$ (MW 258.1644);10) **10**: mp 106 °C, $C_{20}H_{28}O_3$,9) MS m/e 316 (M^+); **11**: mp 156-157 °C, $C_{20}H_{30}O_3$ (MW 318.2174),10) ^{1}H n.m.r. ($CDCl_3$) δ 3.10 (1H, d, J=11 Hz; C-14α H); **12**: mp 228-230 °C, $C_{20}H_{32}O_4$,9) MS m/e 336 (M^+), ^{1}H n.m.r. (pyridine-d_5) δ 3.23 (1H, d, J=11 Hz; C-14α H) and 4.30 (1H, td, $J_{9\alpha,11\beta}$=11, $J_{11\beta,12\alpha}$=11, and $J_{11\beta,12\beta}$=5 Hz; C-11β H); **13**: mp 160 °C, $C_{20}H_{28}O_4$ (MW 332.2000);10)

14: mp 128-129 °C, $C_{23}H_{34}O_6$ (MW 406.2369);$^{10)}$ **15**: mp 165-166 °C, $C_{23}H_{34}O_6$ (MW 406.2353);$^{10)}$ **16**: mp 177-179 °C, $C_{23}H_{32}O_7$,$^{9)}$ MS m/e 420 (M^+), UV (EtOH) λ_{max} 244 nm (ε 12400); **17**: amorphous solid, $C_{22}H_{32}O_6$ (MW 392.2157);$^{10)}$ **3**: mp 200-201 °C (crystallized from ethyl acetate), $C_{22}H_{30}O_6$ (MW 390.1988);$^{10)}$ IR (Nujol) 3400, 1730, 1695, and 1655 cm^{-1}; ^1H n.m.r. ($CDCl_3$) δ 1.00, 1.07 (each 3H, d, J=7 Hz; s-CH_3), 1.11, 1.37 (each 3H, s; t-CH_3), 2.71 (1H, A part of AB-type quartet, J=16 Hz; C-15 $H_{(A)}$), 2.89 (1H, B part of AB-type quartet, J=16 Hz; C-15 $H_{(B)}$), 3.25 (1H, s; C-9α H), 3.93 (4H, m; -$O(CH_2)_2O$-), 4.43 (1H, t, J=3.5 Hz; C-7β H), and 5.53 (1H, dd, J=3.5 and J=2.2 Hz; C-6 H).

References and notes

1) J. Polonsky, Fortschr. Chem. Org. Naturstoffe, **30**, 101 (1973).

2) a) S. M. Kupchan, R. W. Britton, J. A. Lacadie, M. F. Ziegler, and C. W. Sigel, J. Org. Chem., **40**, 648 (1975). b) K. -H. Lee, Y. Imakura, Y. Sumida, R. -Y. Wu, I. H. Hall, and H. -C. Huang, ibid., **44**, 2180 (1979). c) M. C. Wani, H. L. Taylor, J. B. Thompson, M. E. Wall, A. T. McPhail, and K. D. Onan, Tetrahedron, **35**, 17 (1979), and references cited therein.

3) Z. Valenta, S. Papadopoulos, and C. Podešva, Tetrahedron, **15**, 100 (1961).

4) a) J. R. Dias and R. Ramachandra, J. Org. Chem., **42**, 3584 (1977). b) D. L. Snitman, M. -Y. Tsai, and D. S. Watt, Synth. Commun., **8**, 195 (1978). c) N. Stojanac, Ž. Stojanac, P. S. White, and Z. Valenta, Can. J. Chem., **57**, 3346 (1979). d) O. D. Dailey, Jr., and P. L. Fuchs, J. Org. Chem., **45**, 216 (1980). e) G. A. Kraus and M. J. Taschner, ibid., **45**, 1175 (1980). f) P. A. Grieco, G. Vidari, S. Ferriño, and R. C. Haltiwanger, Tetrahedron Lett., **21**, 1619 (1980). g) T. Kametani, M. Chihiro, T. Honda, and K. Fukumoto, Chem. Pharm. Bull., **28**, 2468 (1980). h) H. -R. Schlatter and W. Graf, Helv. Chim. Acta, **63**, 1554 (1980). i) J. Pfenninger and W. Graf, ibid., **63**, 1562 (1980).

5) J. S. Dutcher, J. G. Macmillan, and C. H. Heathcock, J. Org. Chem., **41**, 2663 (1976).

6) R. E. Ireland, S. W. Baldwin, D. J. Dawson, M. I. Dawson, J. E. Dolfini, J. Newbould, W. S. Johnson, M. Brown, R. J. Crawford, P. F. Hudrlik, G. H. Rasmussen, and K. K. Schmiegel, J. Am. Chem. Soc., **92**, 5743 (1970).

7) S. Danishefsky, P. F. Schuda, T. Kitahara, and S. J. Etheredge, J. Am. Chem. Soc., **99**, 6066 (1977).

8) T. Murae, A. Sugie, T. Tsuyuki, S. Masuda, and T. Takahashi, Tetrahedron, **29**, 1515 (1973).

9) Satisfactory result of elemental analysis was obtained for this compound.

10) Determined by high resolution mass spectrometry.

(Received December 25, 1980)