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SYNTHETIC STUDIES ON QUASSINOIDS: A STEREOSELECTIVE CONSTRUCTION OF THE PICRASANE SKELETON

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Summary: 12β-Hydroxypicrasan-3-one, a compound having the correct relative stereochemistry of all the six ring-juncture chiral centers of the picrasane skeleton, was synthesized from a known tricyclic compound, using the orthoester Claisen rearrangement and lead tetraacetate oxidation as key reactions.

A large number of bitter principles isolated from plants of Simaroubaceae family are known as quassinoids,[1] some of which show strong biological activities such as antineoplastics and cytotoxicities.[2] These quassinoids possess a picrasane skeleton (1) or its modified ones and many synthetic studies have been carried out in view of structural and biological interest.[3]

Grieco's group[3a] synthesized (±)-quassin (2) and (±)-castelanolide (3) using intermolecular Diels-Alder reaction for construction of a 9β-H picrasane skeleton, which was then converted into the 9α-H structure; no other groups have yet furnished the complete construction of the picrasane skeleton (1).

We describe below the stereoselective synthesis of 12β-hydroxypicrasan-3-one (4)[4] with picrasane skeleton (1) by use of the orthoester Claisen rearrangement and oxidative ether linkage formation with lead tetraacetate. The retro-synthetic pathway is shown in Scheme 1 (4→5→6→7).

One of us and co-workers reported the synthesis of 8, a compound possessing a 14αH-5-picrasene framework, from an easily available tricyclic ketone (7).[3b] In the present synthesis, we planned a stereoselective introduction of C_2-unit to C-14α position by the orthoester Claisen rearrangement of 6, which was derived from the same ketone (7). Transformation of 7 into 6 was carried out in 59% yield by five sequential reactions [1) $(EtO)_2CO$, NaH/DME 2) $NaBH_4$/EtOH 3) MsCl/pyridine-CH_2Cl_2 4) DBU/THF 5) $LiAlH_4$/THF].

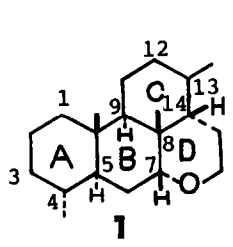
The orthoester Claisen rearrangement of 6 (treatment with triethyl orthoacetate and pentachlorophenol in toluene under reflux for 20h)[5] gave 9, as a sole stereoisomer possessing a two-carbon unit at C-14α position[6] in 88% yield.

Allylic oxidation [CrO_3-pyridine in CH_2Cl_2 or $CrO_2(O^tBu)_2$ in CCl_4] of 9 at C-7 position was first tried to construct the D-ring of picrasane skeleton (1),

but no C-7 oxygenated compound was obtained. Lead tetraacetate oxidation of some appropriate derivative of 9 was then examined. The compound 9 was stereoselectively converted into 5 in 23% yield by five-step reactions [1) $LiAlH_4$/THF 2) Ac_2O/pyridine 3) CrO_3-pyridine/CH_2Cl_2 4) H_2/PtO_2/EtOH 5) KOH/MeOH]. Treatment of 5 with lead tetraacetate in dry benzene under reflux with irradiation of visible lamp gave an oxane derivative (10) as a sole product in 52% yield. The stereochemistry at each of C-7, C-13, and C-14 for 10 was established to be in β-H configuration by NOE experiments using 400 MHz ^{1}H-NMR for 11, which was obtained from 10 by Birch reduction: that is, on irradiation of C-8β-CH_3 protons, methine proton signals assigned to C-7, C-13, and C-14 were enhanced by 7%, 9%, and 7%, respectively , for 11 (see 11a).

The tetracyclic compound 10 was transformed into 4, having the correct relative stereostructure of all the six ring-juncture chiral centers of the picrasane skeleton (1), by successive five-step reactions in 53% yield [1) Li/NH_3/EtOH 2) 2N HCl/THF 3) CH_2=CHOEt/PPTS/CH_2Cl_2 4) Li/NH_3/THF 5) 0.5N HCl/THF]. Stereochemistries at C-4, C-5, and C-12 positions of 4, whose chiral centers were newly introduced during these five reactions, could be deduced from the formation mechanisms and were supported by 400 MHz ^{1}H NMR data.[7)]

Further transformation of 4 into (±)-quassin (2) is under way.



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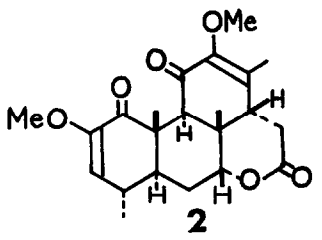

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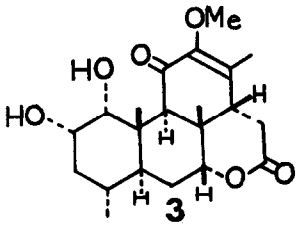

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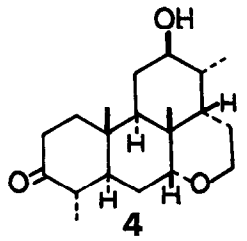
Scheme 1



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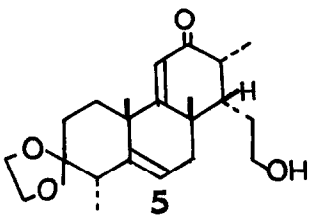

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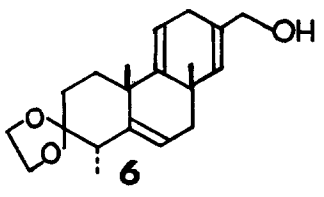

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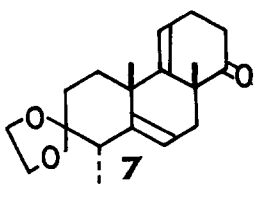

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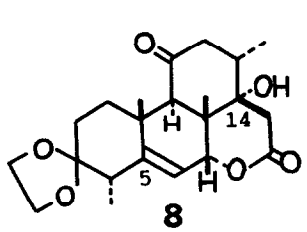

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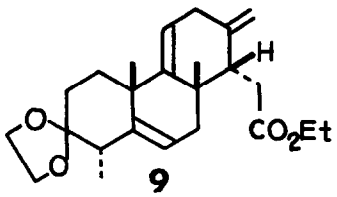

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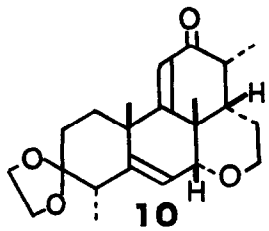

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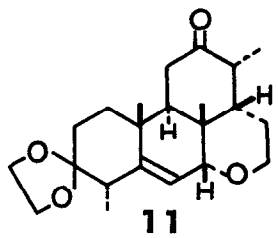

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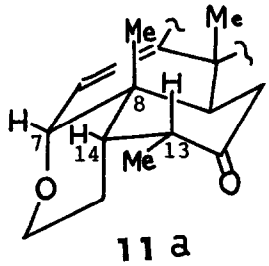

11 a

Characterization of 4-6 and 9-11 is as follows;

4 : crystals, mp 158-160 °C ; IR (KBr) 3450, and 1705 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.97 (6H, d x 2, J=7 Hz), 1.00 (3H, s), 1.10 (3H, s), 2.40 (1H, dq, J=11 and 7 Hz, 4β-H), 3.22 (1H, br s, $W_{1/2}$=8 Hz, 7β-H), 3.35 (1H, td, J=10 and 1.5 Hz, 16β-H), 3.41 (1H, td, J=10 and 4 Hz, 12α-H) and 4.01 (1H, dd, J=10 and 4 Hz, 16α-H); ^{13}C-NMR ($CDCl_3$, 22.5 MHz) δ 11.67, 13.46, 15.28, 22.48 (-CH_3 groups), 22.48, 28.12, 31.39, 37.11, 39.30, 68.50 (-CH_2- groups), 37.11, 41.98, 44.15, 45.23, 50.71, 72.89, 80.12 (-CH- groups), 36.54, 37.30 (-C- groups), and 213.06 (>C=O group); $C_{20}H_{32}O_3$ (m/z 320.2386).

5 : oil, IR (neat) 3500, 1660, and 1600 cm^{-1}; UV (EtOH) 244 nm (ε 8000); ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 1.03 (3H, d, J=7 Hz), 1.15 (3H, d, J=7 Hz), 1.36 (3H, s), 1.44 (3H, s), 3.50 (2H, t, J=7 Hz, 16-H_2), 3.8-4.1 (4H, m, acetal), 5.53 (1H, d-like, J=6 Hz, 6-H), and 5.95 (1H, s, 11-H); $C_{22}H_{32}O_4$ (m/z 360.2314).

6 : crystals, mp 108.5-111 °C ; IR (KBr) 3500 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 1.02 (3H, d, J=6 Hz), 1.18 (3H, s), 1.32 (3H, s), 3.8-3.95 (4H, m, acetal), 4.02 (2H, s, -CH_2OH), 5.3-5.4 (2H, m, 6-H and 14-H), and 5.59 (1H, t, J=3.5 Hz, 11-H); $C_{20}H_{28}O_3$ (m/z 316.2021).

9 : oil, IR (neat) 1740, and 1655 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 90 MHz) δ 1.00 (3H, d, J=6 Hz), 1.14 (3H, s), 1.20 (3H, t, J=7 Hz, -OCH_2CH_3), 1.27 (3H, s), 3.8-3.95 (4H, m, acetal), 4.05 (2H, q, J=7 Hz, -OCH_2CH_3), 4.74 (2H, br s, >C=CH_2), and 5.4-5.6 (2H, m, 6-H and 11-H); $C_{24}H_{34}O_4$ (m/z 386.2462).

10 : crystals, mp 206-208 °C ; IR (KBr) 1680, and 1610 cm^{-1}; UV (EtOH) 241 nm (ε 8600); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.04 (3H, d, J=7 Hz), 1.09 (3H, d, J=7 Hz), 1.32 (3H, s), 1.34 (3H, s), 2.77(1H, q, J=7 Hz, 4β-H), 2.97 (1H, qd, J=7 and 4 Hz, 13β-H), 3.40 (1H, td, J=12 and 3 Hz, 16β-H), 3.53 (1H, d, J=6 Hz, 7β-H), 3.80-4.05 (5H, m, acetal and 16α-H), 5.70 (1H, dd, J=6 and 1.5 Hz, 6-H), and

6.07 (1H, s, 11-H); $C_{22}H_{30}O_4$ (m/z 358.2158).

11 : crystals, mp 183-186 °C ; IR (KBr) 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.96 (3H, d, J=6.5 Hz, 13-Me), 1.01 (3H, d, J=6.5 Hz, 4-Me), 1.07 (3H, s, 10-Me), 1.19 (3H, s, 8-Me), 1.80 (1H, dt, J=13 and 5 Hz, 14β-H), 2.72 (1H, q, J=6.5 Hz, 4β-H), 2.97 (1H, qd, J=6.5 and 5 Hz, 13β-H), 3.35 (1H, td, J=12 and 2 Hz, 16β-H), 3.47 (1H, d, J=6 Hz, 7β-H), 3.75-3.91 (4H, m, acetal), 4.01 (1H, ddd, J=11, 4, and 2 Hz, 16α-H), and 5.55 (1H, dd, J=6 and 2 Hz, 6-H); $C_{22}H_{32}O_4$ (m/z 360.2297).

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References and Notes

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2) e.g.) S. M. Kupchan, R. W. Britton, J. A. Lacadie, M. F. Ziegler, and C. W. Sigel, J. Org. Chem., 40, 648 (1975).

3) a) P. A. Grieco, S. Ferriño, and G. Vidari, J. Am. Chem. Soc., 102, 7586 (1980); G. Vidari, S. Ferriño, and P. A. Grieco, ibid., 106, 3539 (1984); P. A. Grieco, R. Lis, S. Ferrino, and J. Y. Jaw, J. Org. Chem., 47, 601 (1982); idem, ibid., 49, 2342 (1984); b) T. Honda, T. Murae, S. Ohta, Y. Kurata, H. Kawai, T. Takahashi, A. Itai, and Y. Iitaka, Chem. Lett., 1981, 299; c) D. D. Weller and E. P. Stirchak, J. Org. Chem,, 48, 4873 (1983); d) C. Schmidt and T. Breining, Tetrahedron, 39, 3929 (1983); e) R. A. Bunce, M. F. Schlecht, W. G. Dauben, and C. H. Heathcock, Tetrahedron Lett., 24, 4943 (1983); f) S. N. Suryawanshi and P. L. Fuchs, ibid., 25, 27 (1984); g) D. G. Batt, N. Takamura, and B. Ganem, J. Am. Chem. Soc., 106, 3353 (1984); and references cited therein.

4) All compounds reported here are racemic; only one enantiomer related to natural quassinoids is shown for convenience. Nomenclature numberings for all compounds are based on the picrasane skeleton (1).

5) e.g.) F. E. Ziegler, Acc. Chem. Res., 10, 227 (1977); G. B. Bennett, Synthesis, 1977, 589.

6) The stereostructure of 9 was confirmed by the NOE experiments on 11.

7) The ^{1}H-NMR spectra of 4 were also taken under decoupling mode in $CDCl_3$ containing ca. 0.5 equivalent mole of $Eu(fod)_3$-d_{27}. On irradiation of 4β-H (δ 5.13), a signal at δ 4.17 (broad t, J=11 Hz) due to 5α-H changed into a broad doublet (J=11 Hz).

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