Communications to the Editor

Chem. Pharm. Bull.
33(1) 436–439 (1985)

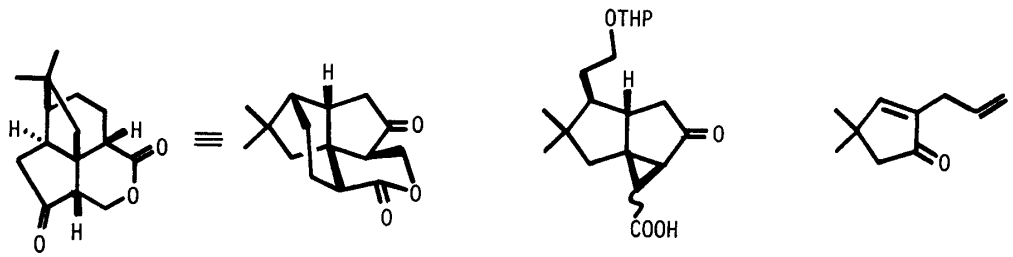
A FORMAL TOTAL SYNTHESIS OF (±)-QUADRONE

Chuzo Iwata,* Masayuki Yamashita, Shoh-ichi Aoki, Kenji Suzuki, Izumi Takahashi, Haruyuki Arakawa, Takeshi Imanishi, and Tetsuaki Tanaka
Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamada-oka, Suita, 565 Osaka, Japan

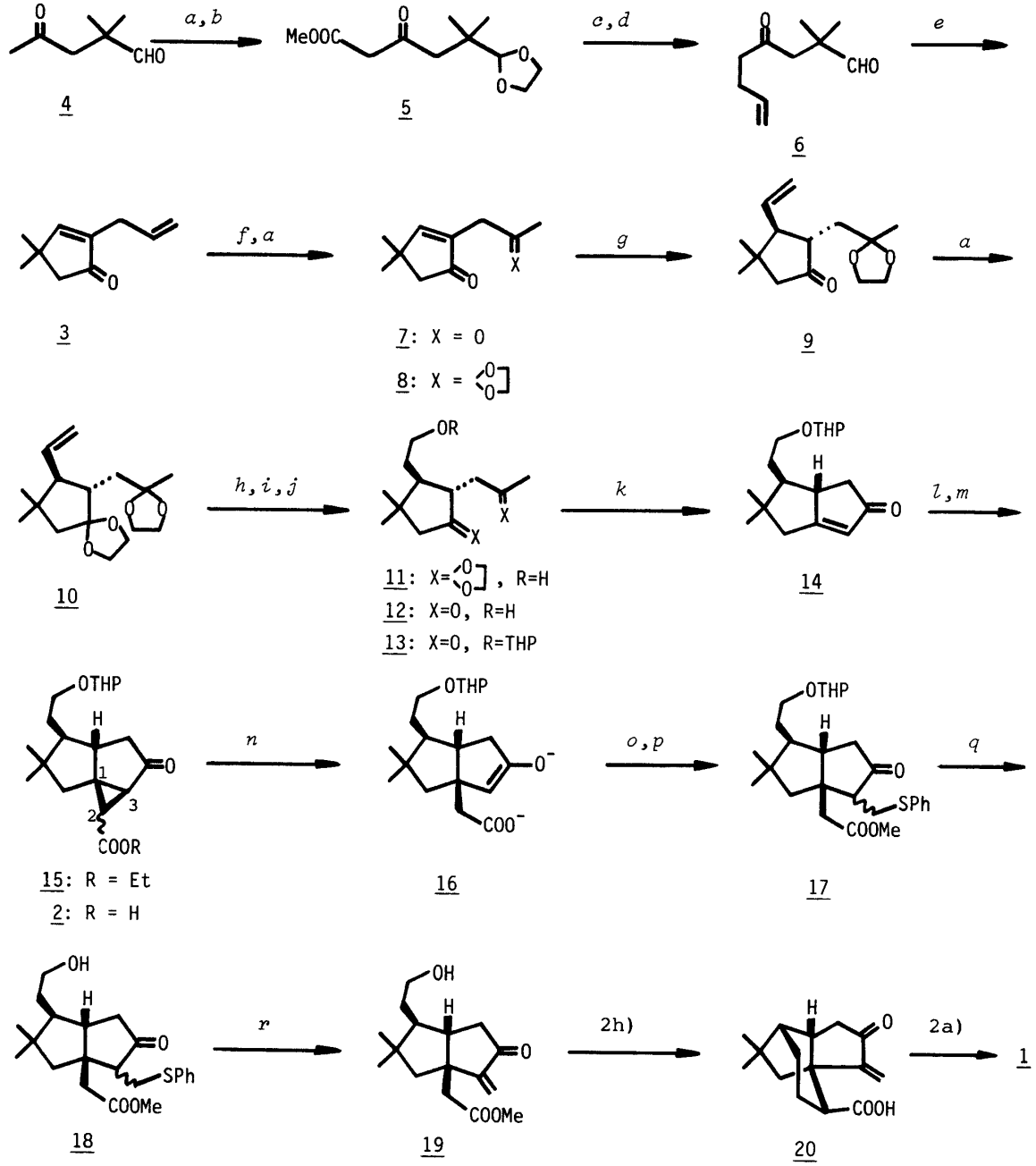
This article deals with a formal total synthesis of (±)-quadrone (1), an antitumor sesquiterpene. The cyclopentenone (3) was transformed into cyclopropane derivative (2), a regioselective reductive ring opening of which and trapping of the enolate intermediate (16) by a C-1 unit afforded the diquinaneacetate (17). By a two-step sequence 17 was converted into methyl (1R*,5R*,6R*)-6-(2-hydroxyethyl)-7,7-dimethyl-2-methylene-3-oxobicyclo[3.3.0]octane-1-acetate (19), which had already been proved to be an intermediate for (±)-1.

KEYWORDS —— formal total synthesis; sesquiterpene; quadrone; terrecyclic acid A; cyclopropane ring opening; cyclopentenone; aldol condensation; regioselective alkylation

In 1978, quadrone (1) was isolated as a metabolite of the fungus Aspergillus terreus and was found to show significant activity against KB human epidermoid carcinoma of the nasopharynx in vitro or against P 388 lymphocytic leukemia in vivo.[1] The unique tetracyclic structure and the potential biological activity of 1 have stimulated great interest in its total synthesis among many organic chemists up to date.[2] In this communication we wish to present a formal total synthesis of (±)-quadrone (1) utilizing a regioselective reductive ring opening reaction of the cyclopropanecarboxylic acid (2), which was stereoselectively prepared from the cyclopentenone (3), and trapping the enolate intermediate (16) by a C-1 unit as a crucial step.



1 2 3



Conditions: (*a*) ethylene glycol, p-TsOH, PhH, reflux. (*b*) dimethyl carbonate, NaH, toluene, reflux. (*c*) allyl bromide, DBU, PhH, 50°C. (*d*) 2N NaOH, 60°C; 50% H_2SO_4, 50°C. (*e*) 10% KOH, THF, reflux. (*f*) $PdCl_2$, CuCl, O_2, DMF-H_2O, r.t. (*g*) vinylmagnesium bromide, CuI-n-Bu_3P, THF, -78°C. (*h*) BH_3, THF, 0°C; H_2O_2, 6N NaOH, 40°C. (*i*) 1N HCl, THF, r.t. (*j*) dihydropyran, p-TsOH, CH_2Cl_2, 0°C. (*k*) NaH, t-$C_5H_{11}OH$, PhH, reflux. (*l*) Me_2S=CHCOOEt, PhH, 45°C. (*m*) KOH, H_2O-ethylene glycol, reflux. (*n*) Li, liq. NH_3, t-BuOH, THF, -78°C. (*o*) $PhSCH_2I$, -78°C. (*p*) CH_2N_2, Et_2O, 0°C. (*q*) p-TsOH, MeOH, r.t. (*r*) $NaIO_4$, MeOH-H_2O, r.t.

2,2-Dimethylpentane-1,4-dione (4)[3] was converted into 2-allyl-4,4-dimethyl-2-cyclopentenone (3) via 5 and 6 in 56% overall yield by the several-step sequence shown in the scheme. The Wacker oxidation of 3 under the usual conditions gave the diketone (7), which was subjected to mild acetalization to afford the mono ketal (8) in 80% yield. The conjugate addition of vinylmagnesium bromide to 8 in the presence of cuprous iodide-tri-n-butylphosphine in THF at -78°C yielded the saturated ketone (9) as a sole stereoisomer in 84% yield. The relative configuration between the C-2 and C-3 substituents was easily derived from similar examples previously reported.[4] The diketal (10), derived from 9 in the usual manner in 75% yield, was hydrated by a hydroboration-oxidation process to afford the primary alcohol (11), which was hydrolyzed by an acid into the diketone (12). After the hydroxyl group in 12 was protected as tetrahydropyranyl ether, 13 was treated with sodium hydride-tert-amyl alcohol in benzene[5] to give the enone (14) in 68% yield without any isomerization of the side chain's configuration. This is the first time that a 2,5-unsubstituted bicyclo[3.3.0]oct-1(2)-en-3-one such as 14 has been successfully obtained by intramolecular aldol condensation.[6] Cyclopropanation of 14 was achieved by the reaction with ethyl (dimethylsulfuranylidene)acetate[7] in benzene and the tricyclononane compound (15) was obtained in 72% yield as a diastereoisomeric mixture dependent on the configuration of the ethoxycarbonyl group. Alkaline hydrolysis of 15 was followed by the regioselective ring opening at C_2-C_3 bond of the cyclopropane and subsequent alkylation. Namely, the carboxylic acid (2) was treated with lithium in liq. ammonia in the presence of one equiv. of tert-butanol and the formed enolate (16)[8] was trapped with phenylthiomethyl iodide followed by esterification with diazomethane to afford the expected product (17) in overall 38% yield from 15. The tetrahydropyranyl part in 17 was removed under a mild acidic condition to yield the corresponding alcohol (18) as a single stereoisomer. On the assumption that the alkyl group attacks from the less-hindered side, the relative configuration between the newly introduced C-1 unit and the methoxycarbonylmethyl group should be cis. Finally, elimination of the phenylthio group by periodate oxidation furnished the key compound (19)[9] in 70% yield from 17. The synthetic product (19) was proved to be identical with the authentic specimen by means of IR and ^{1}H-NMR spectral comparison. Since the enone (19) had already been transformed into terrecyclic acid A (20)[2a] and also into quadrone (1),[2b] the present work constitutes a formal total synthesis of these natural products in racemic forms.

ACKNOWLEDGEMENT The authors gratefully acknowledged the assistance of Prof. S. Isoe (Osaka City University) in supplying the IR and ^{1}H-NMR spectra of (-)-19.

REFERENCES AND NOTES

1) R.L. Ranieri and G.J. Calton, Tetrahedron Lett., 1978, 499; G.J. Calton, R.L. Ranieri, and M.A. Espenshade, J. Antibiot., 31, 38 (1978).

2) a) K. Kon, K. Ito, and S. Isoe, Tetrahedron Lett., 25, 3739 (1984); b) S. Danishefsky, K. Vaughan, R.C. Gadwood, and K. Tsuzuki, J. Am. Chem. Soc., 102, 4262 (1980); idem, ibid., 103, 4136 (1981); c) W.K. Bornack, S.S. Bhagwat, J. Ponton, and P. Helquist, J. Am. Chem. Soc., 103, 4647 (1981); S.D. Burke, C.W. Murtiashaw, J.O. Saunders, and M.S. Dike, J. Am. Chem. Soc., 104,

872 (1982); S.D. Burke, C.W. Murtiashaw, and M.S. Dike, J. Org. Chem., 47, 1349 (1982); S.D. Burke, C.W. Murtiashaw, and J.A. Oplinger, Tetrahedron Lett., 24, 2949 (1983); S.D. Burke, C.W. Murtiashaw, J.O. Saunders, J.A. Oplinger, and M.S. Dike, J. Am. Chem. Soc., 106, 4558 (1984); A.S. Kende, B. Roth, P.J. Sanfilippo, and T.J. Blacklock, ibid., 104, 5808 (1982); K. Takeda, Y. Shimono, and E. Yoshii, ibid., 105, 563 (1983); R.H. Schlessinger, J.L. Wood, A.J. Poss, and R.A. Nugent, and W.H. Parsons, J. Org. Chem., 48, 1146 (1983); J.M. Dewanckele, F. Zutterman, and M. Vandewalle, Tetrahedron, 39, 3235 (1983).

3) P.D. Magnus and M.S. Nobbs, Synth. Commun., 10, 273 (1980).

4) cf. C.J. Sih, R.G. Salomon, P. Price, R. Sood, and G. Peruzzotti, J. Am. Chem. Soc., 97, 857 (1975).

5) J.E. McMurry, A. Andrus, G.M. Ksander, J.H. Musser, and M.A. Johnson, Tetrahedron, 37, Suppl. 1, 319 (1981). For the present purpose, the usual protic conditions, e.g., aqueous KOH/THF, EtONa/EtOH, MeONa/MeOH, tert-BuOK/tert-BuOH, K_2CO_3/EtOH, proved to be unsuitable.

6) E. Piers, B. Abeysekera, and J.R. Scheffer, Tetrahedron Lett., 1979, 3279; M.J. Begley, K. Cooper, and G. Pattenden, ibid., 22, 257 (1981); idem, Tetrahedron, 37, 4503 (1981); D.K. Klipa and H. Hart, J. Org. Chem., 46, 2815 (1981); P. Helquist, Kemia-Kemi, 9, 93 (1982).

7) G.B. Payne, J. Org. Chem., 32, 3351 (1967); B.M. Trost, L.S. Melvin, Jr., "Sulfur Ylides," Academic Press, New York, 1975, pp. 100-105.

8) H.O. House and C.J. Blankley, J. Org. Chem., 33, 47 (1968); G. Stork, S. Uyeo, T. Wakamatsu, P. Grieco, and J. Lavovits, J. Am. Chem. Soc., 93, 4945 (1971); P.A. Grieco, Y. Masaki, and D. Boxler, J. Org. Chem., 40, 2261 (1975); S. Torii, T. Inokuchi, and K. Kawai, Bull. Chem. Soc. Jpn., 52, 861 (1979); Y. Tsuda, N. Kashiwaba, M. Kajitani, J. Yasui, Chem. Pharm. Bull., 29, 3424 (1981).

9) Spectral data of (±)-19. IR (in CCl_4): 3640, 3420, 1742, 1730, 1635 cm^{-1}. ^1H-NMR (in CCl_4): 0.93 (3H,s), 0.98 (3H, s), 2.59 (2H, s), 3.53 (3H, s), 3.62 (2H, t, J = 7 Hz), 5.17 (1H, s), 5.91 ppm (1H, s). UV (in 95% EtOH): 232 nm. High resolution MS m/z: 280.1665 (Calcd for $C_{16}H_{24}O_4$: 280.1672).

(Received November 13, 1984)